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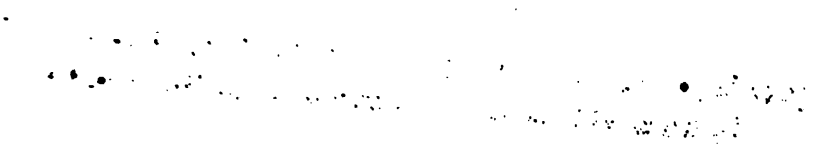

TRANSACTIONS

OF THE

ASSOCIATION OF AMERICAN PHYSICIANS.

SEVENTEENTH SESSION,

HELD AT WASHINGTON, D. C.,

APRIL 29 AND 30, 1902.

VOLUME XVII.

PHILADELPHIA:
PRINTED FOR THE ASSOCIATION.
1902.

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THE Association assumes no responsibility for the statements and opinions expressed in the papers read at its meetings

DORNAN, PRINTER,
701-709 ARCH STREET,
PHILADELPHIA.

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OF THE

SEVENTEENTH ANNUAL MEETING,

Held at Washington, D. C., April 29 and 30, 1902.

THE following members were present during the meeting:

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Isaac Adler,
I. E. Atkinson,
G. Baumgarten,
H. M. Biggs,
Frank Billings,
George Blumer,
B. M. Bolton,
C. S. Bond,
J. W. Brannan,
R. C. Cabot,
Charles Cary,
S. Solis Cohen,
Wm. T. Councilman,
A. C. Cushny,
Elbridge Cutler,
I. N. Danforth,
E. K. Dunham,
A. R. Edwards,
James Ewing,
W. E. Fischel,
Simon Flexner,
M. H. Fussell,
J. P. C. Griffith,
J. B. Herrick,
C. A. Herter,
L. E. Holt,
Wm. T. Howard,
Henry Hun,
H. M. Hurd,
Henry Jackson,
A. Jacobi,
E. G. Janeway,
F. P. Kinnicutt,
J. J. Kinyoun,
Henry Koplik,
H. A. Lafleur,
M. J. Lewis,
Morris Longstreth,
Starling Loving,
S. J. Meltzer,
J. H. Musser,
Wm. Osler,
F. A. Packard,
Wm. H. Park,
G. L. Peabody,
Morton Prince,
T. M. Prudden,
B. K. Rachford,
Walter Reed,
B. Sachs,
G. G. Sears,
F. C. Shattuck,
Wharton Sinkler,
A. H. Smith,
M. A. Starr,
Alfred Stengel,
James Stewart,
J. S. Thacher,
W. S. Thayer,
W. G. Thompson,
W. H. Thomson,
James Tyson,
V. C. Vaughan,
H. F. Vickery,
S. B. Ward,
W. H. Welch,
F. F. Wesbrook,
F. H. Williams,
H. U. Williams,
J. C. Wilson,
C. F. Withington.

TUESDAY, APRIL 29TH—MORNING SESSION.

The meeting was called to order at 10.15 A.M. by President Wilson, who then read the President's Address. (See p. 1.)

The Secretary read the list of nominees recommended by the Council for election to membership.

The Treasurer read his annual report, which was referred to an Auditing Committee consisting of Drs. Starr and Abbott.

The Secretary read a communication from Dr. Carmalt, the Secretary of the Congress of American Physicians and Surgeons, in response to which it was resolved: That the Association vote for a "smoker," with an informal demonstration of specimens, on one evening of the Congress.

It was resolved that the Treasurer be authorized to levy an assessment on each member, if the cost of the next volume of the TRANSACTIONS makes such an assessment necessary.

The following amendment to the Constitution was introduced and laid on the table until the next meeting of the Association for action:

"That the second clause of Article III. of the Constitution and By-Laws, which now reads, 'The number of members shall be limited to one hundred and twenty-five,' be amended so as to read as follows: 'The number of members shall be limited to one hundred and fifty.'" Signed by J. C. Wilson, Wm. Osler, James Stewart, Frank Billings, and S. Solis Cohen.

Dr. Rachford read (for himself and Dr. W. H. Crane, of Cincinnati) a paper entitled "Comparative Toxicity of Ammonium Compounds, a Study in Autointoxication," which was discussed by Dr. Herter.

Dr. Bolton read (for himself and Dr. Carl Fisch, of St. Louis) a paper entitled "An Estimate of the Amount of Toxin in the Blood of a Horse Infected with Tetanus," which was discussed by Drs. Abbott, Meltzer, and Bolton.

Dr. Abbott read (for himself and Dr. N. Gildersleeve, of Philadelphia) a paper entitled "The Etiological Significance of the Acid-resisting Group of Bacteria and the Evidence of Their Botanical Relationship to Bacillus Tuberculosis," which was discussed by Drs. Flexner, Cohen, Meltzer, and Abbott.

Dr. Flexner read a paper entitled "Histologic Alterations of Cytotoxinic Intoxication," which was discussed by Dr. Abbott.

Dr. Vaughan read a paper entitled "A Study of Bacterial Cells," which was discussed by Drs. Meltzer and Vaughan.

Dr. Adler read a paper entitled "Preliminary Note on Some Effects

of Tobacco on the Tissues of Rabbits," which was discussed by Drs. Adami, Herter, and Adler.

Dr. Harris, of Manchester, England, was introduced to the Association.

Dr. Tyson read (for himself and Dr. Croftan) a paper entitled "A Case of Hematoporphyrinuria," which was discussed by Drs. Withington and Starr.

Dr. Herrick read a paper entitled "Pneumococcic Arthritis," which was discussed by Drs. Osler and Musser.

Dr. Howard read a paper entitled "The Pathology of Herpes Labialis and of Herpes Zoster Occurring in Acute Croupous Pneumonia," which was discussed by Dr. Thomson.

Adjourned at 1.25 P.M.

Afternoon Session.

The Association was called to order at 2.50 P.M.

Dr. Vickery read a paper entitled "A Case of Hodgkin's Disease, with Recurrent Fever," which was discussed by Drs. Starr, Kinnicutt, Musser, and Osler.

Dr. Osler read a paper entitled "Splenic Anemia and its Varieties," which was discussed by Drs. Musser, Billings, Cabot, Stengel, Starr, Stiles (by invitation), Cary, Thomson, Kinnicutt, Fussell, and Osler.

Dr. Vickery read a paper entitled "A Case of Albuminuria Associated with Pernicious Anemia," which was discussed by Drs. Musser, Jacobi, and Vickery.

Dr. Thayer read a paper entitled "Acute Polymyositis," which was discussed by Drs. Cabot, Jacobi, and Thayer.

Dr. Lewis read (for himself and Dr. F. A. Packard, of Philadelphia) a paper entitled "A Report of the Cases of Thermic Fever Treated at the Pennsylvania Hospital in the Summer of 1901," which was discussed by Drs. Cabot, Billings, Musser, and Packard.

Dr. Stengel read (for himself and Dr. D. L. Edsall, of Philadelphia) a paper entitled "A Clinical and Experimental Investigation of the Value of Gelatin as a Hemostatic," which was discussed by Drs. Fussell, Peabody, Meltzer, Billings, Tyson, and Stengel.

Adjourned at 5.50 P.M.

Evening Session.

(Held in the Cosmos Club.)

The Association was called to order at 8 P.M. by Vice-President Stewart.

Dr. Bond gave a demonstration of lantern slides illustrating Dr.

Warthin's paper entitled "The Pathology of Pernicious Anemia, with Special Reference to the Changes in the Hemolymph Glands," which, in the absence of Dr. Warthin, were explained by Dr. Flexner, and illustrating Dr. Dock's paper, entitled "Mitosis in Circulating Blood," which, in the absence of Dr. Dock, were explained by Dr. Bond.

Dr. Billings read a paper entitled "Report of the Presence of Anguillula Aceti in the Urine of Two Patients, Mistaken for Strongyloides Intestinalis," which was demonstrated by lantern slides, and was discussed by Drs. Stiles (by invitation), Welch, and Jacobi.

Dr. Ewing then exhibited slides to show the development of vaccine bodies.

Adjourned at 10 P.M.

WEDNESDAY, APRIL 30TH—MORNING SESSION.

The Association was called to order at 10.15 A.M. by President Wilson.

The following physicians were elected to active membership: Dr. A. O. J. Kelly, of Philadelphia; Dr. George M. Kober, of Washington, D.C.; Dr. W. G. MacCallum, of Baltimore; Dr. E. L. Opie, of Baltimore; Dr. E. P. Joslin, of Boston, and Dr. B. W. Sippy, of Chicago.

The following members were elected to honorary membership: Dr. H. M. Hurd, of Baltimore; Dr. Louis Starr, of Philadelphia; Dr. I. Minis Hays, of Philadelphia; Dr. A. Brayton Ball, of New York; Dr. S. A. Fisk, of Denver, and Dr. H. M. Lyman, of Chicago.

The Auditing Committee reported that they had examined the Treasurer's accounts and vouchers, and found them to be correct, which report was accepted.

Dr. Cabot read a paper entitled "The Prognosis of Pleurisy with Effusion," which was discussed by Drs. Osler, Brannan, Harris (Manchester, England), Jacobi, Vaughan, and Cabot.

Dr. Withington read a paper entitled "A Clinical Study of Cases of Empyema Based on the Bacteriologic Findings in the Exudate," which was discussed by Drs. Welch, Prudden, Koplik, Osler, Jacobi, and Withington.

Dr. Fussell read (for himself and Dr. Riesman) a paper entitled "Spontaneous Non-tubercular Pneumothorax," which was discussed by Drs. Kinnicutt, Cohen, Shattuck, Janeway, Peabody, Brannan, Osler, Billings, and Fussell.

Dr. Edwards read a paper entitled "Some Pulsations in the Chest other than Aneurysmal," which was discussed by Drs. Peabody, Jacobi, Lafleur, Cohen, Shattuck, and Edwards.

Dr. Herrick read a paper entitled "Healed Ulcerative Endocarditis," which was discussed by Drs. Thayer, Kinnicutt, Janeway, Shattuck, Jacobi, and Osler.

Dr. Stengel read (for himself and Dr. Stanton, of Philadelphia) a paper entitled "The Conditions of the Heart in Pregnancy," which was discussed by Dr. Fussell.

Dr. Kinnicutt read a paper entitled "A Case of Pancreatic Lithiasis, with the Recovery of the Characteristic Calculi from the Stools, followed by an Attack of Cholelithiasis a Year Later, with the Passage of Characteristic Biliary Calculi," which was discussed by Dr. Janeway.

Dr. Cohen read a paper entitled "A Further Contribution to the Subject of Vasomotor Ataxia," which was discussed by Drs. Prince, Sachs, Jacobi, and Cohen.

Dr. Jackson read a paper entitled "Intestinal Hemorrhage; Its Relation to Duodenal Ulcer," which was discussed by Drs. Kinnicutt, Thomson, and Janeway.

On motion of Dr. Jacobi it was resolved that the Treasurer of the Association be instructed to send the sum of $25 to the Secretary of the American Committee of the Fourteenth International Medical Congress as a contribution toward its expenses.

Adjourned at 1.40 P.M.

Afternoon Session.

The Association was called to order at 2.45 P.M. by President Wilson.

Dr. Shattuck read a paper entitled "Prognosis and Treatment of Tuberculous Peritonitis Based on the Massachusetts General Hospital's Experience for the Past Ten Years," which was discussed by Drs. Tyson, Brannan, Danforth, Billings, Meltzer, Halsted (by invitation), Vaughan, Jacobi, and Shattuck.

Dr. Ewing read a paper entitled "A Pathologic Study of Thirty Cases of Smallpox," which was discussed by Dr. Councilman.

Dr. Park read a paper entitled "Some Experiments on the Nature of Vaccine Virus," which was not discussed.

Dr. Prince read a paper entitled "A Case of Osteitis Deformans and One of Hyperostosis Cranii," which was discussed by Dr. Fussell.

Dr. Sears read a paper entitled "Some Clinical Manifestations of Hepatic Cirrhosis in the Light of Eighty Autopsies," and Dr. Billings read a paper entitled "Clinical Manifestations of the Early Stage of Cirrhosis of the Liver." These two papers were discussed by Drs. Packard, Danforth, A. H. Smith, Herter, and Jacobi.

Dr. Herter read a paper entitled "Experimental Glycosuria from

Adrenalin Chloride, and its Relation to Other Forms of Glycosuria Dependent on the Action of Reducing Substances on the Cells of the Pancreas," which was discussed by Drs. Meltzer, Cushny, and Herter.

During the meeting the following papers were read by title:

"The Action of Metals on Bacteria and Toxins," by F. E. Novy.

"A Diagrammatic Comparison of Types of Bacillus Diphtheriæ in Well Persons and Clinical Cases," by F. F. Wesbrook.

"Report of a Case of Lymphatic Leukemia," by D. D. Stewart.

"The Pathology of Pernicious Anemia, with Special Reference to the Changes in the Hemolymph Glands," by A. S. Warthin.

"Mitosis in Circulating Blood," by George Dock.

"A Case of Cerebral Hemorrhage and Nephritis," by R. T. Edes.

"Two Cases of Supposed Gastric Perforation in which no explanation of the Symptoms was Found at Operation," by A. H. Smith.

"Tuberculous Pericarditis, with Remarks upon Paracentesis and Incision," by Beverley Robinson.

"Drainage in Chronic Intestinal Catarrh; Its Importance and Technic," by Norman Bridge.

"Results of Trauma of the Pancreas," by Charles G. Stockton.

"A Case of Trichinosis Illustrating the Importance of Examining the Blood in Febrile Conditions," by E. G. Cutler.

"A Comparison between the Fluoroscope and Radiographic Examinations in a Case of Dextrocardia," by F. H. Williams.

"A Case of Cystic Degeneration of the Kidneys," by I. N. Danforth.

"Primary Tracheal Diphtheria," by A. McPhedran for R. D. Rudolf.

"Preliminary Report on the Chemical Diagnosis of Suprarenal Tumor," by J. H. Musser.

The following officers were elected:

President—James Stewart.
Vice-President—Wm. T. Councilman.
Secretary—Henry Hun.
Recorder—S. Solis Cohen.
Treasurer—J. P. Crozer Griffith.
Councillors—Charles G. Stockton and Walter Reed.

It was resolved that the Secretary be instructed to return to the Cosmos Club and to the New Willard Hotel the thanks of the Association for furnishing rooms for the meetings.

It was resolved that the thanks of the Association be tendered to Dr. Wilson for his efforts in procuring such a successful meeting.

Adjourned at 6 P.M.

HENRY HUN,
Secretary.

THE PRESIDENT'S ADDRESS.

By J. C. WILSON, M.D.,
OF PHILADELPHIA.

GENTLEMEN: It has been the custom since the founding of the Association for the member whom you have selected to preside at your meetings to open the scientific business of the annual session with some introductory remarks of a general character.

These addresses, as set forth in the volumes of the TRANSACTIONS, are as diversified as they are entertaining. Some treat of the science and art of medicine in the broadest philosophic spirit; others of matters relating to the advancement of the interests of the profession as a body and the increase of its usefulness in an every-day, practical manner. Historic subjects have formed the theme of more than one of these discourses, and he who seeks accurate knowledge relating to contemporary medicine may well turn to these volumes, in which are to be found not only the erudition of the student of medical history, but also an epitome of the best work of the period in pathology and clinical medicine. One admirable address consists chiefly of an analysis of the work of the Association to the time of its tenth session, in 1895. As one would expect in a body like this, made up almost to a man of workers in hospitals either on the side of the wards or that of the laboratories, the principles and details of hospital organization and the subject of hospital abuse have been much considered. Perhaps the most interesting and important portions of many of these addresses, as having a kind of personal bearing, have been those relating to our meetings and our work, and containing suggestions for the present and future welfare of this body.

Were I to have yielded to an early impulse in the matter I would have undertaken an historic subject and spoken of the

growth of medical societies in America and their influence upon the development of the profession as an organization. It would have been agreeable to me, and I trust not unacceptable to you, to have traced the history of the struggle of the American physician to escape from the bondage of his isolation in the earlier periods and the gradual evolution of the idea of a profession. The beginnings were far back—about a century and a half ago. Two organizations—one in Boston, one in New York—but both short-lived, preceded the oldest existing medical society in this country—the Litchfield County Medical Society, of Connecticut, which was founded in 1765, and is still active and flourishing. About the same time—1766—the physicians of northern New Jersey held a meeting at New Brunswick, which was attended by delegates from all parts of the State, and effected a permanent organization, the objects of which, as stated in the preamble to the constitution, were "mutual improvement, the advancement of the profession, the promotion of the public good, and the cultivation of harmony and friendship among the members." This society held regular meetings twice a year until the breaking out of the Revolutionary War. In 1781 the Massachusetts Medical Society was incorporated. Toward the close of 1786 the College of Physicians of Philadelphia was instituted. Other organizations of similar purpose followed from time to time until that memorable meeting of May 7, 1847, at which, by the election of Chapman as President; Knight, Stevens, Moulton, and Buchanan as Vice-Presidents; Stillé and Dunbar as Secretaries, and Hay as Treasurer, the organization of the American Medical Association was finally carried into effect.

The service rendered to the profession, and through the profession to the people, by this great association, with the constituent State and county societies which it has fostered, cannot be overestimated. It has brought the profession together and gives it solidarity. It has not only encouraged the formation and growth of local societies, but has proved a constant stimulus to activity on their part. It has, by means of its section work and excellent *Journal*, set a high standard of professional attainments, and fostered among practitioners a deep sense of responsibility and a lofty conception of the duties and privileges of their calling. But the

very nature of its organization carries with it inherent and serious defects. A body made up of delegates from local societies, supported by members equally devoted to local interests and not especially selected for professional attainments, is necessarily a representative body. Based upon political lines, it is swayed and frequently controlled by political methods rather than by those of science. Ability in the one is mostly developed at the cost of proficiency in the other; hence constant abuses, too obvious to require enumeration or discussion. This fault has been so far recognized as to have led to a reorganization of the Association, by which its general business has been very strictly separated from its work in the sections and intrusted to a house of delegates especially chosen for the purpose. To what extent this arrangement will favorably influence the organization as a whole must be determined by the test of time.

Meanwhile, under the influence of a rapidly developing tendency to specialism, other national societies of more limited scope came into existence upon a wholly different principle of organization. Among the earlier of these were the American Surgical Association, the American Obstetrical Association, the American Gynecological Association, and the body which I now have the honor to address. At the time of the organization of this Association, in 1886, it was proposed to form a Congress of American Physicians and Surgeons by a union of existing special national associations. This proposition was soon carried into effect. Since that period many new national societies have been organized and have become constituent bodies in the Triennial Congresses.

The motive which led to the institution of these associations has never been more clearly and tersely set forth than by Delafield in his brief introductory address. It is the desire to have "an association in which there will be no medical politics and no medical ethics; an association in which no one will care who are the officers and who are not; in which we will not ask from what part of the country a man comes, but whether he has done good work and will do more; whether he has something to say worth hearing, and can say it. We want an association composed of members, each one of whom is able to contribute something real

to the common stock of knowledge, and where he who reads such a contribution feels sure of a discriminating audience."

The recurring meetings and the series of TRANSACTIONS which form the permanent record of our work tell more eloquently than I am able to do how faithfully these purposes have been carried out.

But time presses, and I forbear to dwell further upon a subject which is alike of historic and of present practical interest. The favorable influence of the local and national societies is manifest alike in the medical life of the individual and of the many. Without these societies there could be no organized profession. Without their continuing development and increasing usefulness the progress of medicine will be hampered and retarded.

Death has made sad breaks in the list of our membership. Of one hundred and sixty-four, thirty-five have passed away. The last two of the original seven whom the Association elected honorary members have died during the year that has passed. Among those who have left us several have ceased from their labors early in careers bright with hope, others in the midst of the richest activity and usefulness, and some crowned with honor at the close of long, fruitful lives.

In this last group must be placed the names of the honorary members whom we mourn.

John T. Metcalfe died on January 30, 1902, at the age of eighty-four years. Born at Natchez, Miss., he was educated at West Point and served in the war against the Seminoles in Florida. He subsequently studied medicine at the University of Pennsylvania, and engaged with great success in the practice of medicine in New York. He became Professor of the Institutes and Practice of Medicine in the University Medical College, Physician to Bellevue Hospital, and consulting physician to a number of medical institutions. Dr. Metcalfe was of singularly engaging personality and enjoyed a remarkable popularity, which was due far more to his lofty professional attainments and skill than to his amiable character. He was not a prolific writer, his chief contributions to medical literature relating to the nature and treatment of the malarial fevers and yellow fever; but he was the very type of the practitioner of his day—accomplished, judicious, wise, devoted to the welfare of his patients, faithful to the interests of

his professional colleagues. It is no slight token of the high esteem in which he was held that he was chosen an honorary member of this Association when it was founded, at a period when, by reason of premature infirmities resulting from ill-health, he had for some years retired from active professional life.

Meredith Clymer, whose long career came to a close but yesterday, was also one of the seven original honorary members of this Association. He died in New York on April 20th, at the age of eighty-five years. He was graduated at the University of Pennsylvania—in arts in 1835 and in medicine in 1837. After some years of study abroad he settled in Philadelphia, where he practised medicine for ten years, occupying during this period several teaching positions of importance. He was physician to the Philadelphia Hospital, and had charge of the Cholera Hospital in Philadelphia during the epidemic of 1849. He was for a time Professor of the Practice of Medicine in one of the colleges of Richmond, Va.; and subsequently, having removed to New York, was appointed, in 1850, Professor of the Practice of Medicine in the University of New York. In 1871 he became Professor of Nervous and Mental Diseases in the Albany Medical College. Dr. Clymer was greatly interested in army medical matters during the Civil War, and served during the war and subsequently as Medical Director of the Department of the South.

He was a man of great energy and diversified attainments. His earliest important contribution to the literature of medicine was a treatise upon the fevers. He became especially interested in subjects connected with the nervous system, and his works in this branch of medicine are of value. He was for a period editor of the *Medical Examiner* and associate editor of the *Journal of Nervous and Mental Disease*, and prepared the American edition of Aitken's *Practice of Medicine*. He wrote an oration on Rush and an essay on hereditary genius.

The sudden death of William Waring Johnston came to us, in the midst of the preparations for this meeting, with a shock. He was an original member of the Association, and was earnestly devoted to its interests from the beginning. He found time in a life given to his profession as practitioner, consultant, and teacher to prepare admirable papers for our meeting and to take an active part in our

proceedings. His generous service in arranging the details for these meetings was rendered so modestly that most of us were unaware of our obligation to him. He was long our Treasurer, and at the time of his death a member of the Council. It is not necessary for me in this assembly to undertake to characterize Dr. Johnston as a physician. His high gifts were recognized in the many honorable appointments conferred upon him and in the eagerness with which his services as a practitioner and consultant were sought. He is sadly missed in this city, the especial field of his usefulness. His memory will be affectionately cherished by the members of this Association.

The activity and influence of this Association continues to increase. The number of papers presented is each year greater than can be read. The volumes of the TRANSACTIONS are larger than ever before, and their contents are of the highest scientific value. There is now, as always, a long waiting list of those who crave the distinction of membership, and are worthy of it by reason of ability, training, applicative energy, and personal character.

Permit me to present to your consideration the following suggestions, several of which have been brought forward by my predecessors :

First, that in many instances the form of a communication best suited for publication is not that adapted for presentation to an audience such as this, and that details of clinical histories or of experiments and copious quotations from the literature can often be omitted in the reading of papers without detriment to their value.

Second, that all subjects should be presented with reasonable conciseness. The cost of the volume of the TRANSACTIONS has become so great that the annual dues must be increased or an assessment made to meet it. This year the Council has authorized the Recorder to pursue the latter course if necessary.

Third, that the papers should be handed to the Recorder directly after the meeting or with as little delay as possible. The last volume of the TRANSACTIONS was held back several months on account of the delay in forwarding a small number of the papers.

Fourth, that the wise suggestion of Dr. Da Costa, repeated by our last President, Dr. Welch, in regard to the honorary list be

considered by those "who have been members for a long time, but find it inconvenient to attend regularly, yet wish to remain with us."

Fifth, that the time is now at hand when our membership should be increased to one hundred and fifty.

Sixth, that the number of new members elected in any one year should not exceed ten.

COMPARATIVE TOXICITY OF AMMONIUM COMPOUNDS: A STUDY IN AUTOINTOXICATION.

By B. K. RACHFORD, M.D., and W. H. CRANE, M.D.,
of Cincinnati.

In the beginning we wish to call attention to certain rather well-recognized physiologic facts which have an important bearing on the questions here considered.

The alkalinity of the blood is due to definite quantities of sodium, potassium, calcium, and magnesium, which are so combined in the corpuscles and plasma as to render marked variations in the alkalinity of the blood, either in health or disease, a very unusual occurrence.

The protective mechanism which guards the blood against alkaline loss is so effective that the alkalinity of the blood remains almost constant under nearly all pathologic conditions, even those which are characterized by acid intoxications. In certain severe acid intoxications, however, such as may occur in the last stages of diabetes mellitus, it appears that the alkalies of the blood may be drawn upon to assist in the neutralization and elimination of the enormous quantities of organic acids which are present in the body in this condition.

But from our present knowledge of this subject one seems justified in concluding that the alkalies of the blood are not drawn upon to any considerable extent to neutralize acids in acid intoxications except when so large an amount of the acid is present that it cannot be neutralized by the large quantities of ammonia which are ever present in the tissues, and which constitute, in this regard, a protective mechanism for the preservation of the alkaline bases in the blood.

The ammonia which serves this important purpose of protecting the alkaline salts of the blood from acids has its origin, for the

most part, in the cellular metabolism and retrograde metamorphosis of albumins which are constantly going on. Under ordinary circumstances the amount of ammonia derived from this source appears amply sufficient to neutralize all the acids which appear in the body. There is, however, another source of ammonia in the chemical changes taking place in the formation and absorption of peptones from the intestinal canal. This is shown by the fact that the portal blood contains a large amount of ammonia during the absorption of peptones; and it seems probable that this ammonia, which normally finds its way to the liver and is converted into urea, may in the presence of severe acid intoxications be thrown into the general circulation and assist the ammonia of the tissues in neutralizing acids, thus protecting the alkaline bases in the blood.

The ammonia formed in the tissues is, under normal conditions, combined with CO_2 to form ammonium carbonate, and this is converted by the liver, and possibly other organs, into urea. For this reason only a very small amount of this ammonia, under normal conditions, finds its way to the kidney. It has been estimated that about 1 gram of ammonia is excreted in normal urine every twenty-four hours. The ammonium compounds, therefore, are found in very minute quantities in normal blood.

We do not understand the manner in which all of this ammonia is collected from the tissues and converted into urea, but we do know that under pathologic conditions which result in the presence of acids in the body the ammonia is seized upon by these acids and carried to the kidneys to be excreted. In acid intoxications, therefore, the acid passes through the blood and tissues very largely in combination with ammonium.

The amount of ammonia that may be excreted in combination with pathologic acids is sometimes very great. As much as 8 or 10 grams may be the enormous daily output in such severe acid intoxications as are found in diabetic coma.

For the above reasons it is our belief that symptoms of systemic intoxication which result from the presence of acids in the body are, for the most part, due to the poisonous action of ammonium compounds of these acids rather than to any marked decrease in the alkalinity of the blood which under rare conditions these acids may cause.

Another physiologic fact bearing on this research which should here be noted is that while the alkalies of the blood are not seriously drawn upon for the neutralization of acids until the available supply of ammonia is exhausted, the salts of sodium and potassium, when introduced into the body as medicines, or when, from any cause, they occur in solution in the body media in excess of the quantities required by the blood, are seized upon, in preference to ammonia, by the acids. In acid intoxications, therefore, we may diminish the amount of ammonia excreted in combination with acids by administering the salts of sodium or potassium. The sodium and potassium under these conditions, when introduced from without or when from any cause they occur in excess in the body media, serve to protect the ammonia from the acids and allow it to be converted, as it normally is, into urea, and thus diminish the amount of ammonium compounds in the blood and other body media.[1]

The advantages which may be derived from replacing the ammonium which is being excreted in combination with acids with a base such as sodium will appear later in the discussion of this subject.

AMMONIUM.

In studying the relative toxicity of such ammonium compounds as may possibly occur in the body during health and disease we have thought it advisable in this connection to study the relative toxicity of such salts of the other alkalies as may possibly be found in the body under normal and pathologic conditions, and which may possibly play a rôle in producing the symptoms of auto-intoxications.

The five bases which, under varying circumstances, may be utilized to neutralize acids in the body are ammonium, sodium, potassium, magnesium, and calcium.

The comparative toxicity of the salts which these five bases form when combined with such acids as may possibly be found in the body under normal and pathologic conditions will now be studied.

[1] C. A. Herter. TRANSACTIONS OF THE ASSOCIATION OF AMERICAN PHYSICIANS, vols. xv., xvi., and E. P. Joslin, ibid., xvi., discuss very fully and comprehensively the physiology and pathology of acid intoxications.

The animals used in these experiments were ordinary house mice, and the relative toxicity of the various salts was determined by injecting, from a carefully graduated syringe, a sufficient quantity of 5 per cent. solutions to produce death, and the lethal dose of each salt for a mouse of average size was in this way carefully established.

In this research we have sought to establish not the actual, but the relative toxicity of these salts, and have for this reason classified all salts as relatively "non-toxic" which did not in 10-minim doses produce toxic symptoms. Such salts, we believe, are so feebly toxic that they can play no rôle in producing the systemic symptoms of auto-intoxication, and for the purposes of this research may therefore be considered as "non-toxic."

TABLE I.—AMMONIUM.

Salt.	Toxicity of 5 per ct. solution.		Amount in fatal dose.		Formula.	Relation of weight of base to weight of molecule.		Amount of NH_4 in fatal dose.	
	M.	C.c.	Grs.	Grms.		Ratio	Pr.ct.	Grs.	Grms.
Ammonium oxalate,	3/8	0.04	0.033	0.002	$(NH_4)_2C_2O_4$	18:62	29.0	0.0096	0.00058
carbonate,	2	0.12	0.10	0.006	$(NH_4)_2CO_3$	18:48	37.5	0.0375	0.00225
chromate,	2	0.12	0.10	0.006	$(NH_4)_2CrO_4$	18:76	23.7	0.0237	0.00142
chlorid,	8	0.19	0.15	0.009	$(NH_4)Cl$	18:53	34.0	0.051	0.00306
nitrate,	8	0.19	0.15	0.009	$(NH_4)NO_3$	18:80	22.5	0.0337	0.00202
citrate,	8	0.19	0.15	0.009	$(NH_4)_3C_6H_5O_7$	18:72	25.0	0.0375	0.00225
sulphate,	3.5	0.22	0.175	0.011	$(NH_4)_2SO_4$	18:66	27.3	0.0477	0.008
tartrate,	4.5	0.28	0.225	0.013	$(NH_4)_2C_4H_4O_6$	18:92	19.6	0.0441	0.0025
hydrogen phosphate,	4.5	0.28	0.225	0.013	$(NH_4)_2HPO_4$	18:66	27.3	0.0614	0.0035
acetate,	8	0.49	0.40	0.026	$(NH_4)_2C_2H_3O_2$	18:77	23.4	0.0936	0.00608
sarcolactate,	10	0.62	0.50	0.032	$(NH_4)C_3H_5O_3$	18:107	16.8	0.084	0.00504
lactate,	12	0.74	0.60	0.039	$(NH_4)C_3H_5O_2$	18:107	16.8	0.1008	0.00655

A study of the above table clearly demonstrates the toxicity of ammonium when in combination with most of the ordinary acids which may occur in the body. The importance, however, of the ammonium ions in contributing to the toxicity of certain of the ammonium salts in the above table can better be arrived at by

comparing the toxicity of the ammonium salts of certain acid ions with the sodium salts of the same acid ions. For example, it will be seen by reference to the table of sodium salts that sodium chlorid, sodium nitrate, and sodium sulphate are "non-toxic," while the ammonium salts of the same acid ions are quite toxic. The toxicity, therefore, of these salts, as well as the citrate, tartrate, and acid ammonium phosphate, depends very largely upon the ammonium which they contain.

When ammonium in combination with a comparatively non-toxic acid, such as hydrochloric, is injected subcutaneously into mice the first symptom noted is an increase in reflex excitability, and this is followed by tonic and clonic spasms; but when the toxic dose is not quite sufficient to produce death, then as the convulsive movements subside the respiratory rhythm is markedly disturbed, the breathing is rapid, labored, irregular, and gasping. These symptoms continue for a time, to be followed by a second convulsion, or they may gradually pass off, the mouse entirely recovering.

When, on the other hand, ammonium is combined with a poisonous acid, such as oxalic, the resulting salt, which owes its toxicity largely to the acid ion, will produce a symptom group which differs somewhat from the above description, but which still closely resembles the symptom group of ammonium poisoning.

As has been previously been said, body acids are, as a rule, excreted as ammonium compounds; and in all severe acid intoxications, therefore, large quantities of ammonium in combination with acid ions are diverted from their normal course and made to pass through the lymph and blood channels of the body until they are finally excreted by the kidneys or other excretory organs. By this process the whole nervous system must be directly exposed to the action of these compounds.

From the above facts the inference seems plain that ammonium may be an important factor in producing systemic symptoms in certain acid intoxications; but how important the ammonium ions may be in these intoxications will depend upon the toxicity of the acid ions with which they are combined. In some instances, as we shall see later on in this discussion, the acid ions are much the more important of the two toxic agents, and in others they apparently exert an antitoxic effect on the toxic action of the basic ion.

In this connection it may be well to note that the non-toxicity of the ammonium compounds when given by the mouth may be explained by the fact that ammonium compounds when given in this way do not, as a rule, reach the general circulation, but are converted by the liver into urea.

One of the most interesting facts, however, which is discovered by a study of the above table is that the ammonium ion when combined with an organic acid largely loses its toxicity. The ammonium salts of acetic, lactic, and sarcolactic acids are comparatively non-toxic; these acids when combined with ammonium apparently neutralize or destroy in part its toxic action. It was at first thought that this effect might be more apparent than real, the diminished toxicity being due to the increased molecular weight of these complex molecules and the relatively smaller amount of ammonium which these molecules contained. A reference, however, to the above table shows that these facts fall short of explaining the comparative non-toxicity of the ammonium compounds of the organic acids. It may be noted that the toxic dose of ammonium lactate contains 0.00655 of ammonium, while the toxic dose of ammonium chlorid contains only 0.00306—less than one-half as much. The toxic dose of ammonium lactate is 12 minims of a 5 per cent. solution, and this dose is so large as compared with the toxic doses of the ammonium compounds of the inorganic acids that ammonium lactate may be classified as comparatively "non-toxic." When in connection with the comparative non-toxicity of this ammonium salt one remembers that the ratio of ammonium to the weight of the salt in the molecule is 18 : 107, one can readily understand how very large quantities of lactic acid may be carried in combination with ammonium through the body media, to be excreted by the kidney, without producing symptoms of ammonium intoxication. It may, however, be well to note that while ammonium lactate is comparatively non-toxic, yet feeble as is this toxicity it is much more toxic than sodium lactate.

What is here said of lactic acid applies with almost equal force to all the ammonium salts of organic acids with which we have experimented. The ammonium sarcolactate and acetate have about the same toxicity as the lactate. All of these acids may, therefore, be excreted in considerable quantities without causing

toxic symptoms. These facts may explain the absence of symptoms of ammonium poisoning in diabetes mellitus and other organic acid intoxications. We do not assert, however, that the antitoxic action of the acid ions of the organic acids is sufficient to wholly protect the body against the enormous quantities of ammonia (10 grams in twenty-four hours) which may be excreted in diabetic coma.

SODIUM.

Sodium is not drawn upon very largely to neutralize acids in the body except when it occurs in available solution in excess of the quantity required by the blood or when it is introduced from without as a medicine. Under these latter conditions, however, it is seized upon by acids in preference to ammonia. It may, therefore, when given medicinally, be utilized to protect the ammonia of the tissues, the sodium thus introduced replacing the ammonium in the neutralization of acids. This we believe may, in some instances, be an important substitution, since in this manner the poisonous ammonium salts are withdrawn from the circulation, and the non-poisonous sodium salts are substituted therefor.

TABLE II.—SODIUM.

Salt.	
Sodium chlorid	Ten minims of a 5 per cent. solution produced no result.
" nitrate	" " " " " " "
" sulphate	" " " " " " "
" lactate	" " " " " " "
" acetate	" " " " " " "
Uno-sodium phosphate	" " " " " " "
Di-sodium phosphate	" " " " " " "
Tri-sodium phosphate	" " " " " " "
Sodium sarcolactate	" " " " " " "

In the above table the comparative non-toxicity of sodium compounds for mice is clearly demonstrated, since no symptoms were produced by the injection of 10 minims of a 5 per cent. solution of any of the above compounds. From these facts it seems a fair conclusion that the sodium salts cannot be directly responsible for any of the systemic symptoms which may occur in acid intoxica-

tions. When, however, the acid intoxication is so great that the sodium of the blood is largely drawn upon, and its alkalinity thereby diminished, serious symptoms may follow.

POTASSIUM.

Potassium is a base which when it occurs in available solutions in excess of the quantity required by the blood, or when it is introduced from without, as a medicine, may be utilized in preference to ammonia in the neutralization of acids in acid intoxications. Under ordinary conditions a variable amount of potassium is available for this purpose, and potassium may therefore play a not unimportant rôle in the neutralization of acids even before the available ammonia of the tissues has been exhausted. It is not impossible, therefore, that potassium, which is a poisonous base, may at times contribute to the symptoms produced by acid intoxications.

It should also be noted that in very severe acid intoxications, where the available ammonia has been in great part exhausted, the potassium of the tissues may possibly be drawn upon, in preference to the alkalies of the blood, to neutralize acids.

TABLE III.—POTASSIUM.

Salt.	Toxicity of 5 per ct. solution.		Amount of salt in fatal dose.		Formula.
	M.	C.c.	Grs.	Grms.	
Potassium carbonate . . .	4.0	0.246	0.20	0.012	K_2CO_3
" chlorid . . .	5.0	0.308	0.25	0.015	KCl
" nitrate	5.66	0.349	0.283	0.0175	KNO_3
" sulphate . . .	6.0	0.369	0.30	0.0185	K_2SO_4
" phosphate . . .	6.5	0.400	0.325	0.02	K_2HPO_4
" acetate . . .	9.0	0.554	0.45	0.027	$K(C_2H_3O_2)$

It will be noted in comparing corresponding salts in this table with those in the ammonium table that the potassium has about one-half of the toxicity of the ammonium ion when combined with the same inorganic acids.

The action of potassium in the mouse differs somewhat from that

of ammonium, in that it does not produce violent convulsive action. The symptoms of potassium poisoning in the mouse are rapid and labored breathing, terminating in asphyxia.

The toxic action of the potassium ion should be kept in mind not only because of the possible rôle which it may play as a symptom producer in acid intoxications, but also because in therapeutics we may, by choosing potassium to replace the ammonium ion in severe acid intoxications, only substitute one toxic base for another. From our knowledge of this subject it would appear that "non-toxic" sodium is far preferable to potassium for this purpose.

MAGNESIUM.

Magnesium plays a comparatively unimportant part in the neutralization of acids in ordinary acid intoxications. When, however, a severe acid intoxication has almost exhausted the available supplies of ammonia, then the magnesium of the body may be drawn upon for this purpose. In severe acid intoxications, therefore, such as may occur in diabetes mellitus, magnesium may occur in considerable excess in the urine. For these reasons it may be well to keep in mind that magnesium when combined with acid ions is very toxic. This may be noted in the following table:

TABLE IV.—MAGNESIUM.

Salt.	Toxicity of 5 per ct. solution.		Amount of salt in fatal dose.		Formula.
	M.	C.c.	Grs.	Grms.	
Magnesium chlorid . . .	2.0	0.123	0.10	0.06	$MgCl_2$
" sulphate . . .	8.5	0.215	0.175	0.011	$MgSo_4$

The magnesium compounds produce death in mice very suddenly, without convulsions; they probably paralyze the heart. When, however, a little less than the lethal dose is given the breathing is rapid and irregular for a time, and the mouse, after a period of inactivity, finally recovers. Magnesium has about the same toxicity as ammonium when combined with a sulphate ion, but when combined with a chlorid ion is more toxic.

But notwithstanding the toxicity of magnesium it probably plays an unimportant rôle in producing toxæmia in acid intoxications because of the small amount of this base utilized for neutralizing acids.

The poisonous action of magnesium is unimportant also from a therapeutic stand-point, because when given by the mouth it is absorbed in such small quantities that it cannot be utilized to any extent for replacing the ammonium which is excreted in combination with acids in acid intoxications.

CALCIUM.

Calcium when combined with acid ions has a very slight degree of toxicity, as is shown in the following table:

TABLE V.—CALCIUM AND BARIUM.

Salt.	Toxicity of 5 per ct. solution.		Amount of salt in fatal dose.		Formula
	M.	C.c.	Grs.	Grms.	
Calcium chlorid	6.5	0.40	0.325	0.02	$CaCl_2$
" acetate	10.0	0.616	0.50	0.086	$Ca(C_2H_3O_2)_2$
" lactate	10.0	.....	.....	.....	$Ca(C_3H_5O_3)_2$
Barium chloride	not poisonous 1.5	0.92	0.75	0.004	$BaCl_2$

It appears from this table that, excepting sodium, calcium is the least toxic of the five bases, being notably less toxic than potassium. It is not at all probable that calcium plays any direct rôle in producing symptoms in ordinary acid intoxications, because it is not only very slightly toxic, but is excreted in comparatively small quantities in these conditions. It is believed, however, that calcium plays a rôle as a carrier of the oxalate ion through the blood, the calcium oxalate being kept in solution by the acid sodium phosphate. If this be true, calcium may in this instance be the carrier of a poisonous ion through the body media; but our knowledge of this subject is too vague to justify further inference.

It is possible that the calcium of the blood may be drawn upon, like sodium and potassium, in very severe acid intoxications, and in this way serious symptoms may be produced; but the symptoms

caused by sodium, potassium, and calcium starvation (if such conditions exist) cannot be classified as intoxications directly produced by these bases.

Turning from the rôle which the basic ions may play as symptom producers in acid intoxications, let us now consider the possible rôle which acid ions may play in these intoxications. In such a study it is necessary that these acid ions be combined with some non-toxic base, such as sodium, so that the toxicity of the resulting salt may represent the toxicity of the acid ion alone.

INORGANIC ACIDS.

Sulphuric, nitric, phosphoric, and hydrochloric acids are comparatively non-toxic, as is shown by the fact that the salts produced by their union with a "non-toxic" base, such as sodium, are "non-toxic." From this it would appear that these acids play no important part as direct symptom producers in ordinary acid intoxications.

But, on the other hand, while sodium chlorid, sulphate, phosphate, and nitrate are "non-toxic," ammonium chlorid, sulphate, phosphate, and nitrate are quite toxic; but the toxicity of these salts is largely due to the ammonium they contain. It follows, therefore, that the only apparent rôle which these inorganic acids play as symptom producers in ordinary acid intoxications is as carriers of ammonium, which is brought into the general circulation by their presence in the body.

In cases of acute poisoning by these inorganic acids where large quantities are introduced from without the alkalies of the blood may be attacked, and serious symptoms in this way produced. This condition, however, if it ever occurs, is an indirect effect of these acids, and not due to their poisonous action.

ORGANIC ACIDS.

In certain pathologic conditions organic acids are present in very large quantities in the body, and these acids, for the most part, are neutralized by and eliminated in combination with ammonium; yet these severe acid intoxications, in which large quantities of ammonium in combination with certain organic acids may pass through the blood and other body media on their way to excretion,

may not be characterized by symptoms of ammonium intoxication. Diabetes mellitus is a notable example of this kind. In the advanced stages of this disease we may have as much as 18 or 20 grams of β-oxybutyric acid excreted in combination with 5 grams of ammonium without producing symptoms of ammonium poisoning; and even in the coma stage of this disease, when as much as 8 or 10 grams of ammonia in combination with organic acids are excreted in twenty-four hours, it has not been proven that ammonia plays any rôle in producing the coma, dyspnea, and other nervous symptoms present, notwithstanding the fact that this explanation might be suggested by the disappearance of the coma and other nervous symptoms, when by medication the ammonium, in combination with organic acids, is replaced by a "non-toxic" base, such as sodium.

But whatever may be the explanation of the nervous symptoms in the last stage of diabetes when very large quantities of ammonium in combination with β-oxybutyric acid are circulating through the blood on their way to excretion, the fact remains that prior to the coma stage as much as 5 grams of ammonium in combination with organic acids may, in twenty-four hours, be carried through the blood without producing symptoms of ammonium poisoning. The explanation for this has already been given in the ammonium table, where it is shown that certain organic acids when combined with ammonium neutralize in part its poisonous action. This property of certain organic acids may be noted by a study of the toxicity of the lactates in the previous tables. Lactic acid is an organic acid normally found in the body, which when it occurs in excess is supposed to be capable of producing systemic intoxications; but lactic acid, like uric acid, has obtained this reputation outside of the laboratory. When lactic acid is combined with a "non-toxic" base such as sodium the resulting salt is "non-toxic."

Fifteen minims of a 5 per cent. solution of sodium lactate will not produce toxic symptoms in the mouse. From this it is clear that the lactic acid itself is "non-toxic," and can play no direct rôle in producing symptoms of systemic intoxication. This same acid, as has already been noted, also has the power of partly destroying the toxic action of ammonium when combined with it

to form a salt. This is evident from the fact that it requires 12 minims of a 5 per cent. solution of ammonium lactate to kill a mouse. These facts may explain why even large quantities of lactic acid may be eliminated in combination with ammonium without producing symptoms of ammonium intoxication.

A reference to the ammonium table will show that relatively large quantities of acetic and sarcolactic acid may also be excreted in combination with ammonium without producing symptoms of ammonium intoxication. From this the inference is drawn that ammonium is better adapted for the neutralization of certain organic acids than for certain inorganic salts.

It may also be suggested, in explanation of the fact that large quantities of ammonium may be excreted in combination with certain organic acids without producing ammonium poisoning, that the body has acquired a degree of immunity against the poisonous action of these ammonium salts.

OXALIC ACID.

Oxalic acid when combined with ammonium makes a very poisonous salt; 0.04 c.c. of a 5 per cent. solution of ammonium oxalate will kill a mouse, and this lethal dose contains only 0.00058 gram of ammonium. Ammonium oxalate is, therefore, about four times as poisonous as the ordinary ammonium salts, such as the chlorid.

From these facts it is clear that it is the oxalate rather than the ammonium ion that gives toxicity to this salt, and that oxalic acid poisoning is largely due to the oxalic acid itself, and not to the base with which it is combined. When this base, however, happens to be ammonium the intoxication is more severe. The ammonium ion, while not the most important, is a contributing factor to experimental oxalate of ammonium poisoning.

It appears, therefore, that oxalic acid may be a potent factor in producing systemic intoxication if at any time it be present in considerable excess in the body media. It seems, therefore, rather illogical, in the light of the uncertain chemical knowledge which we have of all the conditions underlying the formation of oxalic acid in the body, and of the form in which it traverses the body media, to assert that oxalic acid—an excess of which in the urine is not uncommonly associated with constitutional symptoms—has

no causative relation whatever to these symptoms. The relationship which oxalic acid bears to these symptoms has perhaps not as yet been definitely determined, although it is an established fact that an excess of oxalic acid in the urine is not always associated with systemic intoxication.

CARBONIC ACID (CO_2).

CO_2 is an acid ion constantly found in the body. The ammonia of the tissues unites with it to form ammonium carbonate, and this salt, in turn, is converted into urea.

A failure of the urea forming function of the liver may, therefore, throw into the general circulation a considerable quantity of ammonium carbonate, which is passed through the blood to be excreted by the kidney.

Since ammonium carbonate possesses a considerable degree of toxicity (see ammonium table), it may be possible that it contributes to the systemic intoxications which occur as a result of the functional inactivity of the liver.

ADDENDUM. BY B. K. RACHFORD, M.D.

URIC ACID LEUKOMAINS.

In a number of papers read before this Association, the first of which was presented in 1895, I held to the opinion that the leukomains of the uric acid group, especially paraxanthin, were important etiologic factors in producing migraine and a number of allied diseases. In these papers I gave in detail the experimental and clinical evidence upon which I based this opinion.

In 1899 Dr. Pfaff read a paper before this Association, entitled "An Experimental Research Indicating that Paraxanthin Poisoning is not the Cause of Epilepsy or Migraine." From this research Dr. Pfaff concluded that the urines from the cases of migraine and epilepsy which he examined did not contain sufficient paraxanthin to produce poisonous symptoms, and he lays especial stress upon the fact that when ammonia was eliminated from his "final fluids" they lost their toxicity. He also suggested from an examination of one of my "final fluids," which contained 17 per cent. of

ammonia, that the toxicity of all of my "final fluids" in my published experiments were due solely to this cause. On this last opinion concerning the toxicity of my "final fluids" I wish to take issue with Dr. Pfaff, for the three following reasons:

First. The specimen of "final fluid" which he examined was not a representative one. At the 1898 meeting of this Association, after discussing this subject with Dr. Pfaff, I agreed to send him one of my "final fluids;" and on my return home I obtained from my laboratory the residue of one of these "final fluids" which had been standing for some weeks. This I sent to Dr. Pfaff, with the explanation that it was one-fifth of a "final fluid" which I had prepared from 2 liters of migrainous urine. One-half of this fluid (one-tenth of my original "final fluid") was used by Dr. Pfaff, and the other half, at my request, was returned to me; and then I learned that the fluid sent to him contained little else than the sediment which was produced when ammonia was added in the final step of making these fluids. This explains the very large quantity of ammonia (17 per cent.) which this fluid contained; and the fact that Dr. Pfaff examined a specimen which represented only one-tenth of one of my "final fluids" (a quantity representing only six or seven ounces of urine) may explain his failure to find paraxanthin in the specimen. However this may be, it is certain, as I afterward wrote Dr. Pfaff, and as I said before this Association in 1899, the "final fluid" in question was not a representative one, as it contained many times more ammonia than the fluids with which I had experimented.

Second. By the method used I uniformly obtained from migrainous urines poisonous "final fluids," and from non-migrainous urines non-poisonous "final fluids." If the faulty technique which I used left in my "final fluids" sufficient ammonia to account for their toxicity, then all of these fluids would have been toxic, and not alone those derived from migrainous urines. The "final fluids" from the very large number of migrainous urines which I have examined must, therefore, have contained toxic ingredients other than ammonia, and these I believe to have been the xanthin bodies.

Third. My "final fluids" retained their toxicity when they contained so small an amount of ammonia that that agent alone

could not have accounted for their toxicity. This fact I presented in the discussion on Dr. Pfaff's paper before this Association, May 4, 1899; and I then detailed some experiments which led me to believe that the ammonium compounds of the xanthin bodies were important agents in producing the autointoxication which is etiologically related to migraine and other lithemic manifestations.

These observations suggested to me the preceding research on the comparative toxicity of such ammonium compounds as may possibly play a rôle in producing symptoms of systemic intoxication, and also encouraged me to further investigate the toxicity of the ammonium compounds of the xanthin bodies.

In these experiments, which I have carried on at intervals during the past two years, I have worked not only with pathologic urines, but also with large quantities (thirty to seventy gallons) of normal urine which I obtained from patients in the Cincinnati Hospital.[1] From these specimens of normal urine I prepared "final fluids" containing the xanthin bodies.[2] After testing the toxicity of these "final fluids" the amounts of ammonia they contained were carefully estimated,[3] and then every trace of ammonia was eliminated from these "final fluids" and their toxicity again tested.

From these experiments I have reached the same conclusions which I expressed before this Association three years ago, namely, that the xanthin bodies were the important toxic principles in my "final fluids," but that their toxicity was increased by small quantities of ammonia in combination with them. The quantities of ammonia, however, required to markedly increase the toxicity of these "final fluids" was much too small to give toxicity to any of the inorganic acid ions studied in this paper.

In this series of experiments the amounts of ammonia in a toxic dose of my "final fluids" varied from 0.0008 to 0.0003 gram.

From these experiments I am prepared to state that the toxicity of my "final fluids" was not due solely to the ammonia they contained, but to other toxic agents found in migrainous but not

[1] In this work I have been assisted by the following resident physicians: Dr. Shaler Berry, Dr. W. H. Stix, Dr. H. L. Woodward, and Dr. B. M. Baehr.

[2] For method see TRANSACTIONS OF ASSOCIATION OF AMERICAN PHYSICIANS, vol. x.

[3] Some of these ammonia estimations were made by Dr. W. H. Crane.

in normal urines, without which the ammonia would have been innocuous.

For these reasons I adhere to the belief that the ammonium compounds of the xanthin bodies gave toxicity to my "final fluids," and that these same compounds are toxic agents in producing migraine and other lithemic disorders which I have described in my previous papers as being due to the xanthin bodies alone.

This opinion seems altogether plausible when one remembers that a functionally incompetent liver, which is an important etiologic factor not only of migraine but of all lithemic conditions, may by the failure of its urea forming function to throw into the general circulation sufficient ammonia to combine with the uric acid leukomains which are also thrown into the circulation by the failure of this self-same function, in this way diminishing the excretion of urea and increasing the excretion of ammonia and the xanthin bodies.

DISCUSSION.

DR. HERTER: There are one or two points in the paper I would like to refer to. I think the study of the toxicity of the various bases and acids is a contribution of no little value. It seems to me, however, that we are not justified at the present time in attributing to the salts of ammonium as found in the organism any peculiar degree of toxicity. By means of the combinations such as Dr. Rachford has pointed out we get a neutralization of the ammonia by the acid ion, but we know of no pathologic condition in which the ammonia excretion is increased, except where the acids are present in excess, or where foods are taken that contain large amounts of acid producing elements.

In regard to the method, I think it would be better to make these comparisons in the toxicity of salts of ammonia with equal molecular solutions instead of percentage solutions.

PRELIMINARY NOTE ON SOME EFFECTS OF TOBACCO ON THE TISSUES OF RABBITS.

By I. ADLER, M.D.,
OF NEW YORK CITY.

It is not the object of the studies of which this is only a preliminary and very fragmentary report to offer a contribution to the toxicology of tobacco or nicotin. They form part of a larger series undertaken for the purpose of investigating the etiology and very early stages of those interstitial and vascular lesions commonly grouped together under the name of arteriosclerosis. For reasons which need not be stated here it was found necessary to investigate the effects of chronic tobacco poisoning. The experiments are still in progress and far from a definite conclusion, still the results thus far obtained may be of some interest. All the experiments are made upon rabbits. The animals are kept in box-stalls, so that they can move about freely, though confined within proper limits. The stalls are littered with excelsior, which the rabbits will not eat, and they are thus compelled to subsist entirely upon the food given them. No stomach tubes or other artificial means of feeding are resorted to, in order to avoid any injury and approximate as nearly as possible to the natural conditions.

The animals are fed exclusively upon fresh cabbage. Each rabbit receives once a day a sufficient quantity of cabbage chopped fine and carefully mixed with an infusion of tobacco. No attempt at exact dosage was made. The infusion is prepared by breaking up cheap cigars (two for five cents) and allowing them to soak overnight in a pint of water, which is then filtered and carefully mixed in increasing quantities from three ounces to half a pint with the day's allowance of cabbage. At the beginning two cigars

to the pint are used, later three, and still later four cigars, so that in the latter months of the experiment each animal consumes a really very large quantity of tobacco juice. In no case has the food been refused, and all the animals, without exception, have eaten every morsel that has been given them without leaving remnants. At first they appear somewhat nauseated and sick, though they move about freely and continue to eat. After a very few days they are perfectly normal, lively, and well. They do not appear to lose in weight, feed greedily, and all their functions are absolutely normal. A female rabbit is at present under observation that has been fed upon tobacco infusion in the manner described for six months, and which consumes at present daily a half-pint of infusion made from four cigars. During this time she has become pregnant and given birth to seven young, everything passing off quite normally. She has nursed her offspring, and is at present stout and apparently entirely healthy. All the rabbits are full-grown, but not old. Their exact age could not be ascertained. Thus far no animal has died, but all appear quite healthy until killed for examination.

A rabbit killed after three weeks of the treatment just described shows no signs of disease anywhere, even upon closest inspection. All the organs appear entirely normal. The stomach is full as usual, and its mucous membrane and the other coats appear healthy. The liver is of normal size, color, and consistency. The kidneys are normal. The bladder is filled with clear, normal urine. Pieces of the liver, kidneys, spleen, pancreas, stomach, intestines, heart, and aorta are, while still warm, placed in a fixing solution, afterward hardened and embedded in paraffin and celloidin. The best results are obtained with Zenker's solution for paraffin and 10 per cent. formalin for celloidin. Careful microscopic examination with the aid of various stains shows all the organs mentioned to be perfectly normal with the exception of the liver, that organ which in experiments of this type is usually the first to show signs of disease. The arrangement of the various component parts of the liver is quite normal, as also are the liver cells. There is no congestion and no degeneration, but surrounding the smaller branches of the interlobular vessels, and especially the smaller bile-ducts, there is a marked, though not

very extensive conglomeration of round cells of the type known as granulation cells. This is very distinct, the more so as everything else is absolutely normal. The central vein of each lobule is entirely free.

An animal killed after two and a half months, apparently in perfect health, presents a somewhat different picture. While all the other organs, macroscopically and microscopically, show no signs of any lesion whatsoever, the liver at once attracts attention. It is decidedly larger than normal, is somewhat paler in color, distinctly granular in appearance, of firmer consistency, and causes a somewhat gritty sensation when cut with a knife. The normal liver of the rabbit, as is well known, contains but very little fibrous tissue, and lobulation is therefore but faintly indicated. In this liver lobulation is very pronounced. There is a very distinct increase of interlobular tissue throughout the entire organ visible in thin sections with the naked eye. The proliferation of the fibrous tissue follows the track of the portal vessels and the bile-ducts. In many places the fibrous tissue is rather firm and hard, contains comparatively few cells, and much elastic fiber. In others it is loose and delicate, carrying abundant round and fibroplastic cells. There is also evident proliferation of the smaller bile-ducts somewhat analogous to human cirrhosis of the liver. The proliferation is well-marked within the lumen, the ducts themselves being frequently closely surrounded by fibrous tissue. The new formation of connective tissue does not extend into the interior of the lobules; it is strictly confined to the interlobular spaces. A most careful study fails to detect the slightest evidence of any lesion of the parenchyma. The liver-cells are absolutely normal, and even in the close neighborhood of the interlobular spaces and the newly forming fibrous tissue show no signs of degeneration or proliferation. The process is restricted entirely to the interstitial tissue and the interlobular spaces.

A rabbit killed while in apparently healthy condition after four months of tobacco treatment presents to the naked eye about the same appearance as the preceding animal. The liver is still large, of the same grayish-red color, but distinctly more granular, harder, and very gritty under the knife. All the other organs appear quite normal. The microscope shows advance of the interlobular

process. The fibrous tissue has increased in bulk and extent. It begins—very sparingly, it is true, but distinctly—to enter between the cells of the lobules. There is a very abundant infiltration of the fibrous tissue with round cells. The new formation and proliferation of bile-ducts has assumed larger proportions. Here and there a small artery can be seen with proliferation of a portion of its intima—a typical picture of endarteritis nodosa. But, notwithstanding all this progressive interstitial activity, the parenchyma, the liver cells, and the central vein remain entirely untouched. There is no change in the cells, no degeneration of any kind; they are thus far absolutely normal, and in nowise participate in the morbid process. Stomach, gut, spleen, and pancreas are normal. In the kidney, however, there may possibly be some incipient change. I have the impression that the first beginnings of an interstitial proliferation of tissue can be made out in several places in the cortex. The changes, if any, are, however, so slight and the subject is so difficult and complicated that it seems better to leave this matter in suspense, awaiting the further development of the experiments. The same holds good for the heart. While the hearts of the preceding animals are unquestionably entirely normal, there is an impression that in the heart of the last animal there may be beginning round-cell infiltration and proliferation surrounding the smaller bloodvessels and capillaries. This seems to be particularly noticeable in the outer layer of the heart muscle, though the epicardium and the muscular tissue immediately adjoining it appear quite normal. Upon this subject also I cannot speak with any assurance; it is as yet merely an impression, and may be quite erroneous.

This is as far as the experiments have progressed up to the present. Whether this interstitial process in the liver is progressive and will ultimately affect the parenchyma? whether an analogy with certain forms of human cirrhosis of the liver will be established? whether other organs will successively participate in this process of interstitial fibrosis, and if so, to what extent? whether the vascular system will also be affected? These and many other questions await solution from further observation, the results of which I hope to report at some future time. I have ventured to present this preliminary note at this early stage of experimen-

tation because it appears that at least one fact even now may be considered as reasonably certain.

A very considerable amount of work has been done on so-called experimental liver cirrhosis and the effects of chronic poisoning on the various organs. The lesions due to alcohol, phosphorus, lead, bacterial, and other toxins have again and again been investigated. There is, however, still disagreement as to results. Where considerable interstitial hyperplasia occurs, as in phosphorus and alcohol poisoning, the liver cells are also affected to such an extent and at so early a stage of the process that it is often impossible to decide which is primary, the interstitial or the parenchymatous affection. It thus happens that opinions differ greatly, some looking upon the interstitial proliferation as caused by and secondary to the primary destruction of the parenchyma cells, while others consider the interstitial fibrosis as primary, and the cell degeneration of the parenchyma as due to the alterations of the interlobular tissue and consequent pressure upon the lobules, interference with vascularization, nutrition, etc. (See Siegenbeek van Heukelom, Ziegler's *Beiträge*, vol. xx., where a very complete and critical discussion of the whole subject up to 1896 may be found.) An unequivocal answer to the question, Are there any toxic agents which primarily, and for a time, at least, solely affect the interstitial and fibrous tissue? is, therefore, of some importance. And this not only with reference to cirrhosis of the liver, but also with regard to more general considerations—arteriosclerosis, for instance. In many of the experiments under consideration there is also some uncertainty as to just how much of the observed lesions is due to the toxic agent employed and how much to gastritis, enteritis, sepsis, and other complications incidentally produced. Comparatively very little experimental work has been done with tobacco. In the literature accessible to me I find only Kohos (*Bulletin Méd.*, Paris, 1897, xi., p. 348) employing methods similar to ours. He gave dogs, guinea-pigs, and rabbits, three to four times daily, 20 to 25 centigrams of tobacco in substance mixed with their food, and continued this for about two months. His description of the histologic changes in his animals, in the very brief notice available, is too short and incomplete to permit any assured deductions. He finds grave

changes both in the liver cells and in the fibrous tissue. In our own experiments we may first of all remark, in passing, the extreme chronicity of the process. This accords well with what is thus far known of chronic tobacco poisoning. Everyone who has given any attention to the subject has remarked upon the tolerance that is shown, both by the human and by animals, to the long-continued abuse of tobacco in contradistinction to the extremely rapid and fulminating course of acute nicotin poisoning. It has not been our object to attempt to determine which of the many constituents of tobacco juice acts as the toxic agent. This would be most interesting work for the chemist. It is quite possible that it is nicotin. Kohos, in his experiments, demonstrated the presence of nicotin in the liver, spleen, heart, and intestines even after tobacco feeding had been interrupted for ten days. It may be that some of the organic acids produce the toxic effects. In this connection it is well to remember that Boix ("Le Foie des Dyspeptiques," *Thèse de Paris*, 1894) succeeded in producing a cirrhotic condition of the liver in rabbits by feeding them with butyric, acetic, and valerianic acids during periods extending from 16 to 387 days. It is quite possible, too, that inorganic substances may play a toxic rôle, and perhaps a combination of a number of substances be necessary to produce just this effect. But however this may be, this much may be safely inferred, that we have in tobacco infusion administered as described a toxic substance, probably one of many, which, acting with extreme chronicity, exerts its influence, at least in the earlier stages, exclusively upon the interstitial and fibrous tissue, uncomplicated by any parenchymatous degeneration or any gastric or intestinal lesion.

DISCUSSION.

DR. ADAMI: Dr. Adler brings forth evidence of a paradoxical nature in his effort to show that the primary disturbance is upon the interstitial substance of the liver rather than upon the liver cells. In the first place, he says that the cells are not affected, and then explains that we have a very marked proliferation of bile-ducts. I think it has been shown that these are not true bile-ducts, but have the appearance more of modified and altered liver cells.

DR. HERTER: I should hesitate to transfer these experiments to the human subject. I do not know that I understood the author to make such a deduction clear, but my impression is that he alluded to it.

DR. ADLER: I was entirely misunderstood by both gentlemen. I have not attempted at all to produce cirrhosis of the liver, nor have I attempted to draw an analogy between what I found and cirrhosis. I said, in closing, that it remains to be proven how much analogy there is between this and cirrhosis. The proliferation of the bile-ducts is certain, as can be seen from my slides. I do not mean bile-capillaries, but bile-ducts, and the proliferation takes place inside of the bile-ducts, where no confounding of liver cells is possible. The only point I wish to make is that there are certain toxic agents that primarily affect the interstitial tissue.

A CASE OF HEMATOPORPHYRINURIA.

By JAMES TYSON, M.D., and ALFRED C. CROFTAN, M.D.,
of Philadelphia.

The patient was first seen December 7, 1901, with Dr. A. McAlister, of Camden, N. J. She is a widow, aged fifty years, the mother of three children, and had always been well until about seven years ago, when she was found to have a uterine fibroid, which was successfully removed a little later. Since then, too, she has been in fair health, although through the entire period she has been taking as a hypnotic 20 to 60 grains nightly of sulphonal, more frequently the larger quantity. Her children reported that they had observed no symptoms of failing health until the last few months, and these were not pronounced. They were, however, aware that for some months the urine had been of an unusually dark color.

On Friday, November 29, she sent for Dr. McAlister, complaining of very severe pain across the upper part of the abdomen, so severe as to require hypodermic injections of morphin, of which at first she received two a day. Under this treatment there seemed to be no abatement of her symptoms, which included constipation. Dr. McAlister had, however, secured one or two unsatisfactory actions of the bowels. Within forty-eight hours previous to our visit her abdomen became markedly tympanitic, assuming a hemispherical shape, something like that of advanced pregnancy.

At the time of the first visit she was found in bed, with dry tongue and appearance of stupor, but still easily aroused and ready to carry on quite a train of conversation if encouraged to talk about herself. The pulse was feeble, its rate about 106, the breathing rate corresponding. The normal liver dulness was obscured by extreme tympany. There was some dark-hued urine at hand, but as

it was evening it was impossible to distinguish tints of color, and it was rather hastily regarded as a bile-stained urine. Placing this fact alongside of the apparently diminished size of the liver, the case was thought to be one of acute yellow atrophy. By daylight, however, the color of the urine proved to be a port-wine red, and on further examination was found to contain a trace of albumin and a small number of pale granular and epithelial casts. Hematoporphyrinuria was immediately suspected.

Sulphonal was introduced into practice as a hypnotic in 1888, and about one hundred cases of hematoporphyrinuria from sulphonal poisoning have been reported since that time. A careful study of many of the case reports shows that in the majority of instances the passage of very dark or of abnormally pigmented urine was considered sufficient evidence of the existence of hematoporphyrinuria; only in a small minority of the cases was the substance isolated from the urine and chemically identified.

The recognition of hematoporphyrin is not difficult. An exact method available for quantitative determinations will be described below. For clinical purposes the following is sufficient:

Barium mixture (consisting of one part of saturated barium nitrate solution and two parts of concentrated baryta water) is added to the specimen of urine; a precipitate forms, containing the bulk of the hematoporphyrin and of other pigments that may be contained in the urine; the barium precipitate is filtered off, washed, and extracted with dilute hydrochloric acid alcohol. If hematoporphyrin is present this extract will be of a reddish or a pinkish hue, and will show fluorescence; if heated on the water-bath the alcoholic solution will turn much darker.

If necessary a spectroscopic examination of the solution may be made that will reveal certain typical features, viz.: a narrow absorption band between C and D in the yellow, and a second, broader band between D and E, between the yellow and the green. If the solution is alkalized, four absorption bands will appear—one between C and D, two between D and E, and a fourth very dark band between b and F, *i. e.*, between the green and the blue of the spectrum. All these features are quite typical and characteristic for hematoporphyrin.

Four specimens of the urine were analyzed, representing the

total quantity voided in twenty-four hours on the four days after the administration of the drug was stopped. The first specimen was of a dark port-wine color, the second one was not quite so dark, the third one was light red, and the fourth was essentially normal in color.

The quantities voided were normal (1560 c.c., 1420 c.c., 1490 c.c., 1500 c.c.). The specific gravity fluctuated between 1018 and 1022, and was therefore normal. The reaction was slightly acid in all four specimens.

The first two specimens contained traces of albumin and a small number of pale granular, hyaline, and epithelial casts. The second two contained no albumin.

None of the samples contained bile pigment, bile acids, urobilin, indican, or sugar. Hemoglobin, or other derivatives of hemoglobin excepting hematoporphyrin, were not detected. The presence of hematoporphyrin was determined by the above method with the aid of spectroscopic tests. The fourth specimen contained only minute traces of hematoporphyrin.

A quantitative test of the hematoporphyrin contained in the first three urines was made as follows:

One hundred cubic centimeters of the urine were alkalized with a dilute sodium carbonate solution and precipitated with calcium chlorid, again alkalized with sodium carbonate, and the precipitate filtered off. The filtrate was yellowish-brown, and showed no spectroscopic bands; the precipitate was colored dark red. The latter was repeatedly washed with distilled water until the filtrate was free from chlorin, then washed with absolute alcohol, and finally extracted with warm dilute hydrochloric acid alcohol. From the pink alcoholic solution the pigment was precipitated with water and the solution neutralized with dilute ammonia. The flocculent precipitate was gathered on a filter and washed with distilled water until the filtrate no longer gave chlorine reactions; then it was washed with absolute alcohol and ether, desiccated over concentrated sulphuric acid *in vacuo*, and finally dried at 115° C. In this way 0.406 gram of a brown, amorphous powder was obtained.

In order to determine how much of this substance was organic —*i. e.*, pigment—and how much inorganic, 0.3845 gram was

heated in a crucible until a constant weight was obtained; there remained 0.2747 gram of inorganic residue. The 0.3845 gram of powder, therefore, contained 0.1098 gram of hematoporphyrin, or 25.9 per cent. One hundred cubic centimeters of urine, therefore, contained 0.105 gram of hematoporphyrin.

One hundred cubic centimeters of the second contained 0.0714 gram of hematoporphyrin; 100 c.c. of the third sample contained 0.006 gram of hematoporphyrin.

Computed for the total quantity of urine, it was found that Specimen I. contained 1.683 gram of hematoporphyrin, Specimen II., 1.013 gram, and Specimen III., 0.098 gram of hematoporphyrin.

These figures enable us to estimate the amount of blood pigment that was destroyed in twenty-four hours in order to furnish these amounts of urinary pigment. Hematoporphyrin has the same empiric formula as bilirubin ($C_{32}H_{36}N_4O_6$). According to Nencki and Sieber (quoted from Salkowski), a given quantity of bilirubin (or of hematoporphyrin) corresponds approximately to an equal quantity of hematin ($C_{32}H_{32}N_4O_4Fe + 2H_2O - Fe$). As hematin contains 9 per cent. of iron and hemoglobin only 0.42 per cent. of iron, 1.63 gram of hematoporphyrin (Sample I.) is derived from 35.1 gram of hemoglobin.

This is a comparatively large quantity of blood pigment, for an adult individual of an average weight of from 60 to 70 kilograms contains about 600 grams of hemoglobin (Salkowski). It will be seen, therefore, that in this case about one-seventeenth of the hemoglobin was destroyed and wasted in the urine during twenty-four hours in the form of hematoporphyrin.

We can well understand how such a loss of blood pigment sustained for a prolonged period of time must lead to severe degrees of anemia.

In our case, happily, the administration of sulphonal was stopped in good time, so that the loss was inhibited, a regeneration of the blood could occur, and the patient recovered.

DISCUSSION.

DR. WITHINGTON: I had a case three or four years ago that was interesting in this connection. A woman, thirty-eight years of age, had diphtheria, for which she received antitoxin, and recovered with a neuritis. She received 15 grains of trional on January 29th, and a second dose on February 1st. The urine in a few days was found to be scanty and bloody, and on February 14th she died. If this condition was caused by trional it was caused only by 30 grains of the drug.

DR. STARR: I can remind the Association of a case reported by an assistant of mine occurring after the use of trional, and I think the coincidence is interesting in connection with the case just spoken of.

THE ETIOLOGICAL SIGNIFICANCE OF THE ACID-RESISTING GROUP OF BACTERIA, AND THE EVIDENCE IN FAVOR OF THEIR BOTANICAL RELATION TO BACILLUS TUBERCULOSIS.

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and

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The following is the account of an investigation conducted in the Laboratory of Hygiene of the University of Pennsylvania between October, 1901, and June, 1902. The expenses incidental to the work were generously defrayed by the Rockefeller Institute for Medical Research, for which the authors here express their indebtedness.

PREFACE.

For a number of years it has been known that bacteria are occasionally encountered which in morphology and staining reactions are so like bacillus tuberculosis as readily to be mistaken for that organism by microscopic methods of study. Through more or less recent investigations our acquaintance with this group has been greatly extended. We have learned that its members are pretty widely distributed in nature; that most of them are susceptible of artificial cultivation; that a number have the power, when deposited in the tissues of certain animals, of causing lesions in many ways suggestive of those of genuine tuberculosis; that in

the course of their growth in the tissues of animals they frequently develop, as is occasionally true of bacillus tuberculosis, after the fashion of the actinomyces or ray fungi, which speaks for their botanical relationship to bacillus tuberculosis; and that, finally, they are frequently encountered upon the fodder and in the excretions and secretions of many domestic animals, some of which are especially prone to tubercular infection. From the foregoing it is evident that we have to deal with a group of bacteria that simulate the exciting cause of tuberculosis to such an extent as to warrant the opinion that they have not only been the cause of error, but are likely so to continue unless we are more or less intimately acquainted with them.

The repeated detection of the members of this group on the food, in the excretions and secretions, and in the surroundings of domestic animals on which we depend for food, renders them of special interest to the practical hygienist. The frequency with which they have been encountered in butter and in milk, for instance, is at once of significance in suggesting such questions as led to this investigation, viz., May not some, at least, of the published statements concerning the presence of tubercle bacilli in milk and butter be due to the mistaking of these organisms for true tubercle bacilli? When present are they to be regarded as but accidental contaminations from the environment under which such products were collected or manufactured, or is it possible for them to have been present as disease-producing factors in the animals from which the milk originally came?

In view of the foregoing facts and questions suggested by them it was deemed advisable to investigate the pathogenic possibilities of this group not only as exhibited upon the small animals ordinarily used for laboratory experimentation, but also upon the larger domestic animals that are susceptible to tubercular infection; to determine their frequency and distribution in butters of various grades and from various sources, and to decide, in so far as possible, their botanical relationship to bacillus tuberculosis. In a number of aspects this problem is but a repetition of work done by others, but in its bearings upon those domestic animals and their products that serve as sources of food-supply it was regarded

as of sufficient importance to warrant careful review. In so far as we are aware, the phase of our work that is, from the practical stand-point, of greatest importance—notably the etiological significance of this group of bacteria for larger domestic animals—has received but little attention from others interested in the subject, and we believe the results of our studies upon this point justify the belief that the confusing, acid-resisting group of bacteria may be dismissed from consideration as probable factors in the causation of tuberculosis or of any condition indistinguishable from it by the ordinary channels through which animals are likey to be infected.

At the time of its discovery bacillus tuberculosis was believed to differ from all other bacteria, except the bacillus of leprosy, in the peculiarity of its staining reactions. When once stained by appropriate methods it is not, as is well known, readily deprived of its color by the ordinary acid decolorizing solutions; it is designated, therefore, as "acid-resisting" or acid-proof ("*sauerfest*"). On this characteristic, probably more than on any other, has reliance been placed in the identification of this organism by microscopic methods.

Shortly after the discovery of bacillus tuberculosis, however, attention was called by Zahn[1] to the presence in the sputum of a non-tuberculous individual of bacilli having more or less the morphology of bacillus tuberculosis, and, like that organism, having the property of resistance to acid decolorization. After another brief interval Alvarez and Tavel,[2] Matterstock,[3] and Bitter,[4] announced as a result of their observations that in the normal smegma there were often to be encountered bacilli of like characteristics; and Cramer[5] and de Giacomi[6] noted the presence of acid-resisting, pseudotubercle bacilli in the normal intestinal contents of man, so that as means of identification the morphology and staining peculiarities of bacillus tuberculosis soon came to be regarded as not infallible.

With increasing frequency during more recent years there have appeared in medical and bacteriological literature additional references to bacteria that in staining reactions and morphology are so strikingly like bacillus tuberculosis as readily to be mistaken for

it on casual examination by the microscope alone, but which may, in most cases, be easily distinguished by their behavior under artificial cultivation and by their effects upon susceptible animals. In a few cases these organisms have been discovered in conditions not entirely above suspicion in so far as the possibility of their having been of tuberculous nature is concerned, but in many instances they were found under circumstances that might reasonably be regarded as having nothing to do with tuberculosis and as unlikely to have been contaminated with tuberculous matters.

Prominent among the group of contributors to this subject, and the conditions under which their discoveries were made, may be mentioned Fraenkel,[7] Pappenheim,[8] and Rabinowitsch,[9] who noted the occurrence of these confusing organisms in the sputum from cases of pulmonary gangrene; Laabs[10] and Moeller,[11] who detected them in the saliva of non-tuberculous individuals; Dietrich,[12] who found them in a suppurating ovarian cyst; Petri,[13] Rabinowitsch,[14] Hormann and Morgenroth,[15] Grassberger,[16] Herbert,[17] Weissenfeld,[18] Korn,[19] Ascher,[20] Coggi,[21] Herr and Beninde,[22] and Tobler,[23] who record their more or less frequent occurrence in butter; Moeller,[24] who found them upon certain sorts of fodder and in stable manure; Severin,[25] who discovered them in the dung of horses, Capaldi,[26] in that of cows, and Ferran,[27] in that of cows, horses, and man; and, finally, Cowie,[28] who has shown them to be fairly frequent in the smegma about the vulva, mammæ, or anus of normal cows, horses, dogs, guinea-pigs, and white rats.

From the foregoing it is evident that the members of this group are widely distributed, and because of the manifest likelihood of their leading to error are worthy of careful consideration.

It is needless at this time to dwell upon the details of the thirty odd organisms of this group that have been found microscopically and isolated in pure culture. It will suffice to say that when studied in pure culture they do not apparently represent more than, at most, two species, the rest being but varieties, possessed of certain fundamental group characteristics. The bacillus of leprosy, probably the most important of the organisms simulating bacillus tuberculosis, cannot with certainty be said to have been cultivated, nor has leprosy or anything like it been reproduced in animals by the inoculation of leprous tissues. *Bacillus smegmatis*,

probably identical with the so-called bacillus of syphilis, can be cultivated only by special methods, but, so far as we know, is without disease-producing power, though in this respect it has received little attention. The balance of the group, frequently encountered under conditions of saprophytism, may be isolated and grown artificially. In some cases they are isolated readily, in others with difficulty; the reason for the difficulty being, as a rule, that the suspicious bacilli are present with other more rapidly growing species, and are so in the minority that their separation from the other species by culture methods often results in failure. In the case of those occurring in butter but little trouble is usually experienced. When, for instance, butter containing them is injected into the peritoneum of guinea-pigs conditions are created, through the irritating action of the fatty vehicle, that favor their growth. Under these circumstances they are almost uniformly capable of causing pathological lesions, and may with little difficulty be isolated from such lesions in pure culture unless, as occasionally happens, other pathogenic species be at the same time present in the butter injected.

Though resistant to decolorization by acids, this peculiarity is by no means absolute, and the results of our studies upon this phase of the subject lead us to believe that many if not all of the members of the group may be at once distinguished from bacillus tuberculosis by their comparatively low resistance to acid decolorizers. All of them, it is true, retain their color for longer or shorter periods when acted upon by such acid-decolorizing solutions as acetic acid (5 per cent.) and alcohol, hydrochloric acid (3 per cent.) and alcohol, sulphuric acid (5 per cent.) in water; but they lose it almost instantly if treated by the nitric-acid solution (25 to 30 per cent. in water), employed in the original Koch-Ehrlich process for the microscopic identification of bacillus tuberculosis—a fact that in our experience serves at once to distinguish them from genuine tubercle bacilli.*

In morphology the members of this group, whether they be susceptible of artificial cultivation or not, are in certain phases of their development strikingly like bacillus tuberculosis. They are

* See Cowie. The Physician and Surgeon, Detroit and Ann Arbor, January, 1902.

seen as short, slender, usually beaded rods, in some cases being almost identical in form and size to the tubercle bacillus. (See Fig. 1, *a* and *b*.) In a few instances the only point of resemblance is their resistance to decolorization by acids. Occasionally they are clubbed or bulbous, sometimes a little spindle-shaped; but in nearly all cases they are sufficiently suggestive of tubercle bacilli to cause confusion if found microscopically in very small numbers in a specimen of urine, milk, or butter, for instance, especially if the staining method of Gabbet or of some one or another of the comparatively weak acid decolorizers had been employed. In this connection we should not lose sight of the fact that the morphology of true tubercle bacilli is occasionally seen to deviate from that given in the classical descriptions of it, though its staining characteristics remain fairly constant.

When studied under conditions of artificial cultivation those that are capable of growth, which would probably include those most widely distributed, are at once easily distinguished from the exciting factor of tuberculosis. All grow more or less readily at from 20° to 22° C., and all, with the possible exception of those found in coldblooded animals, quite readily at 37° to 38° C. Some grow more rapidly than others, but all much more rapidly than bacillus tuberculosis under similar conditions. For instance, a growth of bacillus tuberculosis under the most favorable conditions is rarely seen earlier than from seven to ten days after transplantation; while with the confusing group growth, even to the extent of distinct colony formation, is commonly seen in from thirty-six to forty-eight hours—sometimes a little earlier, sometimes a little later, but never so delayed as to be confused from this stand-point with the tubercle bacillus.

The character of the growth, too, is quite distinct; but from our studies the difference is more often one of degree than of kind. The growth of bacillus tuberculosis upon artificial media is, as is well known, characterized by the occurrence of coarse, hard, granular masses that can only with difficulty, if at all, be broken up in fluids so as to form a homogeneous suspension; while that of the confusing group begins and continues as a dry, wrinkled, rapidly spreading, lustreless layer that subsequently takes on in some cases a pale or even distinct salmon color, in others a decided

orange hue. If this layer be examined optically and by the sense of touch the hard granules that characterize the growth of bacillus tuberculosis will be missed; but it is interesting and important to note that, though absent, their place is taken by a uniformly mealy condition of the growing mass that impresses one as but a low degree of the conspicuously granular development of bacillus tuberculosis.

For the purposes of this contribution it is needless to dilate upon the development of this group upon special media or their various biological functions under particular conditions of cultivation.* It suffices to say that on solid media favorable to their growth and to that of bacillus tuberculosis there is no likelihood of their being confounded with the latter organism by anyone at all familiar with it.

PATHOGENESIS.

The effect of this group of bacteria on animals is variable, depending upon the animal used, the mode of inoculation, and the quantity of culture employed. When injected beneath the skin of rabbits or guinea-pigs, even in such large doses as from 0.5 to 1 c.c. of an opaque suspension, there is, as a rule, either no result or there is subacute suppuration of the neighboring lymph glands.

If pure cultures be injected into the peritoneal cavity, and the dose be not excessive—*i. e.*, not more than 1 c.c. of an opaque suspension—there is often no result; but if there be injected into the peritoneal cavity of either rabbits or guinea-pigs a small quantity of some such aseptic irritant as sterilized butter, and this be followed by an injection of the bacteria in pure culture, an extensive, sometimes fatal, fibrinopurulent peritonitis usually results.† From this the organism used may be recovered in pure culture. It is important to note that by this procedure, as well as

* For a comparative study of the biology of some of the members of this group, see Pettersson, Berl. klin. Wochenschr., 1899, Jahrg., xxxvi. s. 562.

† It has been suggested that the part played by the butter is not so much that of an irritant, preparing the way for the bacteria by causing points of lessened resistance, as that of a protective, shielding the bacteria from the germicidal action of the living tissues by enclosing them in a fatty envelope. It seems to us that it may be both.

after the injection of butter in which these organisms are accidentally present, the lesions of the peritoneum and the peritoneal surface of the abdominal viscera are often marked by small, round, or oval nodules that have somewhat the appearance of tubercles. Histologically, however, the nodules resulting from this mode of inoculation partake more often of the suppurative than the true tubercular character, though by certain observers they are said to occasionally resemble true tubercles to such an extent as scarcely to be distinguished from them.

By injection directly into the testicles of guinea-pigs, with the view of forcing the bacilli into the abdominal lymphatic circulation, the results may be negative or may result in suppuration at the site of injection. If, on the other hand, sterile butter be injected into the peritoneum of an animal so treated there usually occurs a wide-spread fibrinopurulent peritonitis, marked by nodular formations containing acid-resisting bacteria.

In our experience, the most convenient and satisfactory method of studying the pathogenic possibilities of the members of this group is by intravascular injection. If one inject into the circulation of the rabbit, by way of the vein in the ear, for instance, a moderately large dose (1 to 1.5 c.c.) of a suspension of either of the typical members of the group—viz., "butter bacillus" (Rabinowitsch), "grass bacillus II." (Moeller), or "timothy hay bacillus" (Moeller)—there appear in from twelve to eighteen days, with a fair degree of regularity, larger and smaller nodules in the internal organs. Some of these—the smaller and younger ones—are often difficult, if not impossible, to distinguish from genuine tubercles of the same age by either macroscopic or microscopic examination; while others—more particularly those that are further advanced—are characterized more by exudative than by proliferative and necrotic tissue changes.* The peculiar distribution of these nodules not only attracts attention, but at once serves to distinguish the process from that following upon the similar inoculation of animals of the same species with genuine tubercle bacilli. In the latter event there is usually an involve-

* For an excellent description of these nodules from the histological stand-point, see Hölscher, Münchener med. Wochenschr., 1901, s. 1483.

ment of all the internal viscera, with the lesions sometimes more numerous and conspicuous in one than another organ, but under all circumstances the lungs are more or less conspicuously affected; while the results following upon the injection of the confusing group of bacteria are in the vast majority of cases confined, singular to say, to the kidneys. Involvement of the lungs, in our experience, has been the exception; for instance, of forty-five rabbits into the venous circulation of which were injected opaque suspensions of these organisms in amounts ranging from 0.5 to 1.8 c.c. only seven developed pulmonary lesions. The animals were killed in—roughly stated—from fifteen to twenty-two days after the operation. Twenty-three of these rabbits were inoculated with Moeller's grass bacillus II., and the lungs of two were involved; eleven received injections of Rabinowitsch's butter bacillus, and suspicious nodules were found in the lungs of one; and eleven were inoculated with Moeller's timothy hay bacillus, and four suffered from lesions of the lungs; while of four rabbits treated in the same way with suspensions of genuine bacillus tuberculosis marked pulmonary involvement was detected in all. In one of these latter animals, killed as soon as ten days after the inoculation, both lungs were found studded throughout with young, easily recognizable miliary tubercles.

We did not in a single instance detect disease of the spleen, liver, myocardium, or diaphragm in animals inoculated with the confusing group of bacteria. In two cases tiny foci of suppuration were found in the brain. These were not subjected to systematic study in serial sections, but in sections taken at random neither acid-resisting bacteria nor bacteria of any sort were detected by microscopic examination. No cultures were made.

On microscopic study of the nodules resulting from injection of *bacillus tuberculosis* one finds, as is well known, miliary and conglomerate tubercles having all the histological peculiarities of those seen in tuberculosis of man, including true giant cell formation, though this is apparently somewhat less common in experimental tuberculosis of rabbits than in tuberculosis occurring spontaneously in human beings. On histological study of the nodules occurring in rabbits after intravenous injection of the acid-resisting bacteria the conditions found are inconstant. Occasionally nodules

are encountered that, both to the naked eye and in their histological structure, are almost indistinguishable from true tubercles, being characterized by central necrosis, giant-cell formation, proliferation of epithelioid and lymphoid cells, and the customary reaction of the surrounding tissues. This is particularly the case in the early stages of development. More often, however, this typical appearance is not encountered. To the naked eye the nodules may to some extent suggest tubercles, but on microscopic study they are found to be characterized more by suppurative and exudative changes than by the proliferative and progressive necrotic reactions peculiar to true tubercular infection, and this difference becomes more and more evident as time advances.

We have observed no tendency to progressive destruction of tissue through the fusion of neighboring nodules, as is so characteristic of tuberculosis; and we have no grounds for believing that the infection becomes general through the transportation of bacilli, by way of the blood or lymph channels, from the foci of disease to other organs and tissues—a very significant difference, as is also noted by Hölscher (*loc. cit.*)—between tuberculosis and this type of infection. When occurring in the lungs—which, as stated, is comparatively infrequent—the lesions observed by us in different animals have varied considerably from one another in their histological peculiarities.

Sometimes the nodules, save for their numerical infrequency and their lack of tendency to dissemination or fusion, could scarcely be distinguished by their individual structure from true tubercles. They were marked at the centre by a kind of necrosis (not typical caseation); there was proliferation of the fixed tissue cells, and marked exudative phenomena or leucocytic invasion were absent. In other cases they were suggestive of tubercles without being very like them. In one case they were characterized so much by proliferation of lymphatic tissue, with little invasion of leucocytes and but limited necrosis, as to leave little room to doubt that it was but a reaction of the normal lymphatic structures of the organ. In another case (intravenous inoculation with timothy bacillus) the lung was marked by several yellow, sharply isolated areas, ranging in size from 2 to 4 mm. in greatest diameter, that were irregular in outline and sharply differentiated from the surrounding healthy

lung tissue. Macroscopically they presented little to suggest tuberculosis; in fact, we were disposed at the autopsy to regard them as either foci of suppuration or as possibly of animal parasitic origin. On microscopic study these areas proved to be very sharply separated from the surrounding healthy lung tissue, and to constitute lesions partaking in some respects of the character of tuberculosis, in others of ordinary granulation tissue. Scattered throughout them were numerous giant cells of various sizes, some lymphoid tissue, and many islands of closely packed polymorphonuclear leucocytes. The most conspicuous feature, however, was the presence of large, stellate mycelia of most unusual appearance. One can best comprehend their structure by likening them to chrysanthemums of microscopic dimensions. In some cases the mycelia were surrounded by epithelioid cells in a more or less active state of proliferation (Fig. 2), giving the picture of giant cells in their formative stage, marked at their centre by the growing fungus; in others, in addition to the proliferating epithelioid cells, the fungus was encompassed by a more or less dense zone of polymorphonuclear leucocytes.

The lesions of the kidneys, which in rabbits are practically constant, may be described as follows: In animals killed twelve to eighteen days after intravenous inoculation of moderately large doses of either of the type organisms the kidneys are found, as a rule, marked by small yellow or gray points. Sometimes these are scarcely larger than a pin-point, are circumscribed, and do not project above the surface of the organ; again, they may be as large as a small pin-head, may be distinctly yellow in color, may stand up prominently from the cortex, and in some cases be so intimately adherent to the capsule that the removal of the latter tears them bodily from the organ. This is not, however, always the case. At times they do not extend to any considerable distance into the organ, while in other cases they may penetrate a millimetre or so into the cortex. On section of the organ they are often found scattered through it, some being confined to the pyramidal portion. To the naked eye only the smallest of these nodules would be mistaken for tubercles. The larger, and particularly those elevated above the surface of the organ, are much more suggestive of miliary abscesses. On microscopic examination, also, some of these nod-

ules in the early stages of their development are almost indistinguishable histologically from true tubercles, but later on they become marked by a degree of leucocytic invasion that converts them into foci having many of the peculiarities of low-grade suppuration. In brief, the characteristics of the lesions are those of the so-called "foreign body" tubercles.

In all cases the lesions, from the anatomical stand-point, are like tubercles in that they are isolated nodular points surrounded by more or less unaffected tissue; in that they are characterized in their earliest stages by proliferation of the fixed cells of the tissues, and later by a certain degree and kind of necrosis; and in that they are occasionally marked by giant-cell formation. They are unlike tubercles in the absence of any tendency to fusion, metastases, or dissemination; in the ultimate occurrence of suppuration or organization rather than in progressive destruction of tissue by caseation; and in their occurrence, after introduction into the veins, more often in the kidneys than in any other organ of the body.

From the stand-point of the exciting factors it may be said that when in the tissues of a susceptible animal the tendency of bacillus tuberculosis is to disseminate; the disease caused by it is progressive; metastases are regularly seen, and wherever they occur are characterized by destruction of tissue by caseation. This is not the case with the pseudotubercle bacilli under consideration. They remain where deposited, and though they may develop actively at these points, there is no tendency for their effects to extend beyond very narrow confines or for the bacilli to be distributed in an active state through the blood and lymph streams.

THE EFFECTS OF THE ACID-RESISTING BACTERIA UPON LARGER DOMESTIC ANIMALS.

Through the important investigations of Theobald Smith,[29] of Koch,[30] and of Ravenel[31] we have learned that the genuine bacillus of tuberculosis varies in its pathogenic properties according to the source from which it is obtained and according to the animals on which it is tested, cultures obtained from bovines, for example,

being, as a rule of higher degree of virulence than those from man, so that we are beginning, because of this difference, to speak of bovine tubercle bacilli and of human tubercle bacilli.

Through a series of studies during the past decade we have become acquainted with another type of tubercle bacillus—one that affects especially birds. This organism—the so-called bacillus of avian tuberculosis—causes in birds a disease having many of the characteristics of genuine tuberculosis, but it is practically without disease-producing potencies for mammals.

More recently we have learned of the occurrence of tubercle bacilli, or of bacilli like them, in fish and other cold-blooded animals; and from several sources evidence has been presented in favor of the opinion that tubercle bacilli of mammalian origin may become modified in certain respects by a sojourn in the tissues of animals of other classes.

In consideration of these facts we have endeavored to discover if the acid-resisting organisms that simulate bacillus tuberculosis differ likewise in their pathogenic potencies in different species of animals. In this connection it is manifestly of importance to determine their relation not only to the small animals used in the laboratory, but also to those domestic animals that are susceptible to tuberculosis and on which we rely for certain articles of food. With this in view our investigations were made upon hogs and calves. In taking up this phase of our subject the only account of similar studies that came to our notice is that of Sato and Brauer.[32] These investigators injected into the peritoneal cavity of each of two calves 100 c.c. of a bouillon culture of an acid-resisting bacillus obtained by them from butter. They suspected its identity with the butter bacillus of Rabinowitsch, though they did not determine this certainly.

One of these calves received only the culture, the other the culture followed by 100 c.c. of sterile melted butter. In the first calf the results were negative; in the second three large tumors partaking of the nature of granulomata were found in the peritoneum at autopsy.

In both cases the animals were killed thirty-five days after inoculation.

Our own experiments and results were as follows:

EXPERIMENTS ON HOGS.

In this series of studies the grass bacillus II. of Moeller was selected not only because it may be taken as a type of the group of acid-resisting bacteria, but because of its habitat and because of the regularity with which pathological lesions suggesting tubercles are produced by it in rabbits and guinea-pigs by particular methods of inoculation.

Four small hogs, about one-third grown, were selected from an unsuspicious source. They were tested with tuberculin, and none reacted.

On November 13, 1901, two cubic centimetres of a thick suspension of grass bacillus II. were injected into the loose cellular tissues of the right groin of each of two of them, and on November 14th the same quantity of the same suspension was injected into the groin of a third, while the fourth pig was kept as a control. The suspension of bacilli injected was made from the entire surface growth from a slanted glycerin-agar culture that had grown for seven days at 37° C. The origin of this culture was a suppurating nodule in the testicle of a guinea-pig produced by injection of grass bacillus II. on October 31st. By culture methods the material injected into the hogs was found to be a pure suspension of the organism under consideration. After injection the four pigs were kept in cages in the laboratory stalls, two in each cage, and were fed daily on measured quantities of suitable food. The food was not sterilized. The animals throve and at no time evidenced any results of the inoculation.

On January 8th, fifty-five days after inoculation, one of the pigs was killed. At the time of inoculation it had weighed 15.11 kilo.; when killed it weighed 25.49 kilo., so that there had been a gain in weight of 10.38 kilo.

At autopsy there was found a conspicuous deposit of subcutaneous fat. There was no involvement of the subcutaneous lymphatic glands, even of those nearest the site of inoculation, and subsequent microscopic study showed them to be normal. On opening the abdomen the omentum was found marked by a considerable deposit of fat. The small intestines and mesenteric lymphatics were normal. On the rectum, about 5 or 6 cm. from the anus,

were two nodules, one about 5 mm., the other about 15 mm. in diameter. These proved to be abscesses containing creamy pus. They were located beneath the serosa, and in the case of the larger, communicated with the lumen of the intestine. On microscopic examination the pus was found to consist, in the main, of granular débris, a few well-formed polymorphonuclear leucocytes, and ordinary bacilli. No acid-proof bacteria were to be found. By culture methods the bacilli seen proved to be of the colon group. They were not studied in detail. Two guinea-pigs were inoculated with the pus. The one that received the subcutaneous inoculation died in twelve days of general infection. Cultures of bacilli of the colon group were obtained from the spleen and peritoneal cavity. The other, that received an intraperitoneal injection of 1 c.c. of a bouillon suspension of the pus, showed no effects. After twelve days it had gained 60 grammes in weight; it was then killed. The results of the injection as seen at autopsy were negative. The liver, spleen, lungs, heart, and left kidney of the hog presented no deviations from the normal. In the right kidney was a congenital cyst of about the size of a pigeon's egg. It was filled with clear urine. In short, the animal was not in any way affected by the inoculation.

January 23d, seventy days after inoculation, killed small sow. At the time of inoculation she weighed 15.06 kilo.; when killed her weight was 29.28 kilo., making a gain of 14.22 kilo.

Autopsy. Thick deposit of subcutaneous fat. No involvement of subcutaneous lymphatics. Moderate amount of fat in the omentum. Stomach and intestines normal. At one point in the mesentery was a small cluster of lymphatic glands that seemed to be unusual in size, but showed no other change. They were examined microscopically after preservation in Orth's fluid and alcohol, and found to be normal.

Liver, spleen, lungs, and heart normal.

Both kidneys presented a number of small, round, unelevated gray areas of about 1 mm. in diameter. These were plainly visible on the cortical surface after removal of the capsule. They had a little the appearance of young miliary tubercles, but on subsequent microscopic examination they all proved to be collections of lymphoid elements. There was nothing about them to suggest

either proliferative or exudative process, and we therefore regarded them as lymph nodes, probably normal to the organ.

Cultures from the mesenteric lymphatics and from the spleen were negative.

As in the foregoing animal, nothing was found that could properly be referred to the inoculation. In short, the animal appeared normal throughout.

On January 28th the third pig, a small boar that had received a subcutaneous inoculation on November 13th, was found to have gained 10.63 kilo. in the seventy-five intervening days. At no time had it shown any inconvenience attributable to the operation. This, together with the negative results obtained in the first two animals, suggested the advisability of a more radical experiment. On January 28th, therefore, we injected directly into the lung of this animal, and also into that of the control animal, through the thoracic wall, 13 c.c. of a suspension of the same organism. The suspension injected represented the entire surface growth from three well-developed slanted glycerin-agar cultures. The animal experienced no inconvenience either at the time of the injection or afterward. It was killed February 10th, thirteen days after the intrapulmonary injection, and showed at that time a further gain of 0.31 kilo.

Autopsy revealed a thick layer of subcutaneous fat. The subcutaneous lymphatics and the internal organs except the right lung, into which the injection had been made, did not deviate in their appearance from the normal. At the point of puncture of the needle the right lung was adherent to the parietal pleura by several bands of fibrous tissue. Scattered through this tissue, and also at a number of points in the thickened pleura, were isolated yellow points varying in size and shape. The substance of the lung, even in the vicinity of the site of inoculation, showed no nodules, and except immediately beneath the thickened pleura there was no evidence of an inflammatory condition; in brief, it was normal in appearance. On its thoracic surface the diaphragm was adherent to the lung at two isolated points. At three points the new-formed tissue gave the appearance of being acutely inflamed. These were marked by several small more or less circumscribed yellow areas, about which there was a certain degree of

reddening. In all cases these isolated points presented more the appearance of suppurating nodules than of those common to tubercular infection.

On closer study, both by cover-slips at the autopsy and by sections of the hardened tissue, they were found to consist of accumulations of polymorphonuclear leucocytes and enormous numbers of acid-resisting bacteria. In the thickened pleura the acid-resisting bacteria were not only massed in these inflammatory foci, but were widely distributed throughout the communicating lymphatics. In none of the sections were nodules encountered that had the least resemblance to tubercles or to the nodules following upon intravenous injection of rabbits with the acid-resisting organisms.

The bacteria in the tissues presented no characteristic grouping. They were commonly to be seen in dense, irregular clumps, but in no case was actinomyces-like development observed. They were often encountered within the bodies of leucocytes.

On January 23d the fourth pig, which had up to that date served as control, was weighed and found to have gained 13.93 kilo.

On January 28th there was injected directly into its right lung 12 c.c. of a bouillon suspension made from the entire surface growth of three well-developed slanted glycerin-agar cultures of grass bacillus II. There was no immediate result, and the animal was not apparently inconvenienced by the treatment. After fifteen days it was killed, and on weighing before killing it was found to have lost 5.74 kilo. since the inoculation. This is the only one of the four animals on which the general effect of the inoculation was manifested by loss in weight. But it must be remembered that an enormous quantity of material had been injected into its lung.

At autopsy essentially the conditions noted in the third animal were found. There was a marked deposit of subcutaneous and omental fat. The lymphatics neither subcutaneous nor mesenteric were affected. The internal viscera were normal with the exception of the lung into which the injection had been made. This was adherent to the parietal pleura at the point of puncture of the needle, and immediately about this point the pleura was somewhat thickened and marked by a number of elevated yellow areas of from 3 to 4 mm. in diameter. In neither this nor the preceding

animal was there any visible deposit of fibrin or fibro-pus on the pleura.

On microscopic examination of both fresh and hardened preparations the yellow nodules upon the pleura and in the new-formed adhesion bands were found to consist of masses of leucocytes and acid-resisting bacilli. The latter were very inconstant in length, were conspicuously beaded, were often clubbed, and were frequently within the bodies of the leucocytes.

The lung was also adherent at one point to the diaphragm.

By both macroscopic and microscopic examination the lung itself showed no involvement except immediately beneath that part of the pleura in which the inflammatory reaction was most pronounced. Even here there was nothing to be seen in the way of nodules that might be mistaken for tubercles. The change, such as it was, consisted of a limited amount of diffuse inflammatory reaction.

As in the preceding animal, microscopic examination of sections of the thickened pleura and the contained yellow areas showed the latter to consist of sharply circumscribed masses of polymorphonuclear leucocytes and acid-resisting bacilli in large numbers. At many places the latter almost filled the lymphatic spaces in the immediate neighborhood of the suppurating focus. Nowhere was their development or grouping characteristic; they were seen simply as separate rods and threads or as irregular clumps of them.

In both this and the preceding animal Moeller's grass bacillus II. was recovered in pure culture from the nodules on and in the pleura.

Cultures from the site of inoculation of the first two animals that had received subcutaneous injections were negative, and cultures from the internal organs of all four animals (except the right lungs of animals Nos. 3 and 4) were uniformly negative.

From the foregoing we regard it as a justifiable conclusion that the grass bacillus II. of Moeller, which may be fairly regarded as a typical member of the group of pseudotubercle bacteria, is practically without pathogenic properties of importance for one of the domestic species that is constantly susceptible to tuberculosis by similar methods of inoculation. It seems unlikely, therefore, that this organism, when gaining access to the bodies of these animals

by the customary portals of accidental infection and in the ordinary numbers, can be regarded as of etiological significance in exciting conditions that may be mistaken for tuberculosis. That such potencies may be exhibited under peculiar predisposing conditions is, of course, not beyond the realm of possibility; but this would probably occur only under an unusual group of conditions —conditions with which we are at this time unacquainted.

INTRAVENOUS INOCULATION OF CALVES.

Six calves were used for this test.

On March 22, 1902, three calves were inoculated intravenously, by way of the left jugular vein, with the *timothy hay bacillus* of Moeller, and three in the same manner with the *butter bacillus* of Rabinowitsch. The amount of culture injected into the circulation of each animal of this series was the entire surface growth from two well-developed slanted glycerin-agar cultures of the organisms used. The cultures were ten days old, having grown for six days at 37.5° C. and for four days at ordinary room temperature. For each injection the bacteria were suspended in from 12.5 to 15 c.c. of sterile bouillon.

Each animal was subjected to the tuberculin test before it was inoculated, and again before it was killed, with negative results in every instance.

None of the animals of this series gave evidence during life of inconvenience from the inoculation. With one exception they all gained in weight at an apparently normal rate. The gains ranged between ten pounds for Calf No. 7 and forty-seven pounds for Calf No. 12. Calf No. 13, the single exception, lost fifteen pounds in the interval of thirty-three days between the date of its inoculation and the termination of the experiment.

Two animals of the series were killed on the twenty-second and four on the thirty-third day after inoculation. In not a single instance did the post-mortem examination reveal the presence of lesions that could be referred to the bacteria with which the animals had been inoculated, and the blood and internal organs were free from living bacteria, as determined by cultures.

The protocols in more or less detail for these animals are as follows:

Calf No. 1.—Inoculated March 22, 1902. 15 c.c. of a bouillon suspension made from the entire surface growth of two glycerin-agar cultures of butter bacillus (Rabinowitsch) were injected into the left jugular vein of this animal. When inoculated the calf weighed 282 pounds; when killed, twenty-three days later, it weighed 296 pounds, making a gain of fourteen pounds. Tuberculin tests before inoculation, and again just before the animal was killed, gave negative results. Twenty-three days after inoculation the animal was killed, and careful examination failed to reveal the existence of any conditions attributable to the treatment the animal had received. By macroscopic examination it was apparently normal throughout. Cultures were negative.

Calf No. 2.—On the same date there was injected into the circulation of this animal the same dose of the same organism as was employed in Calf No. 1. Before inoculation this animal weighed 315 pounds; just before it was killed it weighed 325 pounds, making a gain of 10 pounds in thirty-three days. This calf was subjected to the tuberculin test both before inoculation and immediately before it was killed, with negative results in both instances. It was killed thirty-three days after inoculation.

At autopsy no lesions were found in any of the organs that could be referred to the inoculation; in fact, the viscera were normal throughout, except the right lung, in the upper lobe of which were found a number of small, sharply circumscribed, firm, red and reddish areas, having somewhat the appearance of hepatization. On examining these areas more closely a number of the bronchi were found to be plugged with muco-pus and to contain embedded in this pus actively motile, white, thread-like worms measuring 2.5 to 3 cm. in length, and being of about the thickness of ordinary sewing-thread, sometimes a little thicker. At times only a single one of these worms would be found in a bronchus, while, again, they were present in large tangled masses. It is evident from the foregoing that we have to deal here with the condition of ordinary verminous pneumonia occasionally seen in cattle. Microscopic examination of sections from the diseased portions of this lung failed to reveal the presence of acid-resisting bacteria or of actinomyces, and cultures were negative in so far as the growth of acid-resisting organisms is concerned.

Calf No. 3.—This animal was treated in precisely the same way as Calves 1 and 2, the same organism having been used for the inoculation. At the time of the injection it weighed 363 pounds; just before it was killed, thirty-three days later, it weighed 388 pounds, making a gain of 25 pounds. It was subjected to the tuberculin test both before inoculation and again just before it was killed, with negative results in both instances.

It was killed April 23d—that is, thirty-three days after inoculation—and was found at autopsy to be normal. There were neither lesions attributable to the inoculation nor lesions of any other sort detectable by careful macroscopic examination. Cultures from this animal were negative.

Calf No. 4.—On March 22d, 12.5 c.c. of a bouillon suspension containing the entire surface-growth from two well-developed glycerin-agar cultures of Moeller's timothy hay bacillus were injected into the circulation of this

animal by way of the left jugular vein. At the time of inoculation this calf weighed 229 pounds; just before it was killed it weighed 269 pounds, making a gain of 40 pounds in twenty four days.

At autopsy nothing was discovered in any of the organs that could have been referable to the bacteria injected. Cultures from blood were negative.

Calf No. 5.—This animal was inoculated in precisely the same manner as was Calf 4, the same organism having been used. At the time of the inoculation it weighed 293 pounds; thirty-three days later, when it was killed, it weighed 340 pounds, making a gain of 47 pounds. It was subjected to the tuberculin test both before inoculation and before it was killed, with negative results in both instances. It was killed April 23d, thirty-three days after inoculation.

At autopsy no lesions were found that could be reasonably referred to the inoculation. In both kidneys were a number of irregularly outlined, gray or yellow, depressed areas, having much the appearance of scars. They ranged in size between those not larger than a pin-head to those of from 5 to 6 mm. in their greatest diameter. Sometimes they were superficial, but more often they extended a slight distance into the cortex of the organ. They were much paler than the surrounding tissue; were sharply outlined; there was no apparent reaction of the tissues about them, and in general they were homogeneous in structure, as seen in fresh sections through them. In no particular did they suggest tubercular or suppurative processes. Microscopic examination of these areas revealed a collection of lymphoid cells and some increase of interstitial connective tissue, but no foci of suppuration or caseation. Cultures were negative.

Calf No. 6.—This animal was treated in identically the same manner as Calves 4 and 5 and with the same organism. At the time of inoculation it weighed 300 pounds. It was killed thirty-three days later and found to weigh, just before killing, 285 pounds, making a loss of 15 pounds. It was subjected to the tuberculin test both before inoculation and a few days before it was killed, with negative results in both instances.

It was killed April 23d, thirty-three days after inoculation, and nothing whatever of a pathological nature was found in its internal viscera. Cultures from the blood were negative.

INTRAPULMONARY INOCULATION OF CALVES.

In this test nine animals were used. Five of them were inoculated with Moeller's grass bacillus II., two with butter bacillus (Rabinowitsch), and two with Moeller's timothy hay bacillus.

In all cases the material was injected through the thoracic wall directly into the lung by means of a hypodermic syringe provided with a long needle.

The doses employed varied, the smallest being approximately one-third of a large wire loopful of the surface growth of a

glycerin-agar culture of Moeller's grass bacillus II. suspended in 2.5 c.c. of bouillon, the largest being the *entire* surface growth of two slanted glycerin-agar cultures (ten days old) of butter bacillus and of timothy hay bacillus suspended in from 12.5 to 15 c.c. of sterile bouillon. In no instance were the animals inconvenienced by the injections.

With two exceptions (Calves No. 9 and No. 12) all gained in weight, the gains ranging between one pound in two months for Calf No. 11 and fifty pounds in three months for Calf No. 7. Calf No. 9 lost twenty pounds in three months, and Calf No. 12 two pounds in eighteen days.

As in the case of the preceding series, all the animals of this group were tested with tuberculin before they were inoculated, and all again before they were killed, with negative results in every instance.

The results of the inoculations were negative throughout in so far as the production of conditions simulating tuberculosis is concerned. The protocols of the autopsies in more or less detail are as follows:

Calf No. 7.—November 13, 1901. Injected into the right lung of this calf, weighing 425 pounds, 2.5 c.c. of a bouillon suspension of Moeller's grass bacillus II. The suspension was made by mixing six very large wire loopfuls of well-grown agar-agar cultures of the organism in 20 c.c. of bouillon. The cultures used had uniformly caused pseudotubercles when injected into the circulation of rabbits. The calf exhibited no inconvenience from the injection.

It was killed February 14th—*i. e.*, three months after inoculation. At that date it weighed 475 pounds, making a gain of 50 pounds during the three months following the inoculation.

Autopsy. The abdominal viscera were normal. A number of pale points were seen upon the cortices of the kidneys that in general suggested miliary tubercles. A number of these were dissected out, mashed between cover-slips and stained. Microscopic examination showed them to be uniformly free from bacteria. Cultures were also made from a number of them, but no acid-resisting bacilli developed. Sections of the organs preserved in Orth's fluid and in alcohol showed these nodules to be collections of lymphoid cells. No exudative and no necrotic processes were observed in any of them, nor were bacteria detected in any of the sections. We concluded from this that, as in the case of the hogs, these pale areas probably represented normal lymph nodes. This opinion was strengthened by finding similar pale points in fresh calf's kidneys purchased from the butchers in the open market. No

deviations from the normal were detected in any of the other abdominal organs, and none in the heart, pericardium, or left lung.

The right lung, beyond a slight increase of fibrous tissue on the pleura at the point of needle puncture, showed no change whatever. At no place were nodules, either suppurative or suggestive of tubercular infection to be detected.

Microscopic examination of the lung at about the point of inoculation showed it to be free from disease; neither necrotic nor suppurative foci being detected anywhere. There was no bronchitis and no increase of the lymphatic tissue about the bronchi.

Calf No. 8.—On the same date there were injected into the right lung of a calf of 257 pounds 2.5 c.c. of the same suspension that was used on Calf 7. This calf was also killed on February 14, 1902. At time of inoculation it weighed 257 pounds, when killed it weighed 275 pounds, making a gain of 18 pounds in the three months interval.

Autopsy. All the internal organs were normal except the inoculated lung. Numerous pale points similar to those found in the kidneys of Calf 7 were found in the kidneys of this animal. These, as in the case of Calf 7, were sterile, and on section were found to be more or less isolated collections of lymph cells, from which all evidence of suppurative or necrotic processes were absent. The pleura of the right lung at the site of inoculation was thickened and marked by several small nodular elevations about 2 to 4 mm. in diameter, that to the touch gave the sensation of hard bodies located some distance beneath the surface.

On microscopic examination of sections through the thickened pleura and the adjacent lung the nodules were found to be in the lung tissue just beneath the pleura and to be due to a localized condition of purulent bronchitis, with considerable increase of peribronchial lymphatic tissue. Some of the bronchi and bronchioles were filled and distended with closely packed polymorphonuclear leucocytes.

No bacteria were found in any of the sections. The surrounding lung tissue was healthy, and there was nowhere to be found anything that either closely or remotely suggested tubercular infection.

Calf No. 9.—On the same date a third calf received an intrapulmonary injection of 5 c.c. of the same suspension of grass bacillus II. When treated this calf weighed 260 pounds, when killed, three months later (February, 14th), it weighed 240 pounds, making a loss of 20 pounds in the interval between the beginning and the termination of the experiment.

Autopsy.—On opening the abdominal cavity the only suspicious condition noted was an apparent enlargement of the mesenteric lymphatic glands. Subsequent microscopic study of these, however, showed them to be free from disease. The abdominal viscera were normal throughout.

The kidneys presented similar pale areas (from 1 to 2 mm. diameter) to those noted in Calves 7 and 8, and, as in the cases of those animals, they proved on microscopic examination to be isolated collections of lymphoid tissue and by cover-slip and cultural methods to be free from bacteria. The heart and left lung were normal.

The right lung, into which the injection had been made, was adherent to the thorax at the site of inoculation by several small bands of fibrous tissue. At its posterior edge it was also adherent over a small area to the diaphragm. To the naked eye it presented, even at the adherent points, little or no deviation from the normal beyond a slight thickening of the pleura. At the point of adhesion to the thorax, entangled in the new-formed tissue, was a nodule about the size of a bean. This proved on closer examination to be a lymphatic gland. There was a moderate invasion of polymorphonuclear leucocytes, some increase of lymphatic tissue, but no isolated areas of suppuration or of caseation, and but little evidence of inflammatory changes in general in this gland.

Sections of the inoculated lung, made as nearly as possible through the point of needle puncture, showed the lung tissue to be unaffected. There were no nodules, no isolated areas of suppuration, and no evidence of diffuse inflammatory changes. The pleura was a little thickened, but was not marked by any isolated points of suppuration or caseation.

Neither in sections of the lung nor pleura were bacteria of any sort found.

Sections through the other portion of the lung that was adherent to the diaphragm gave essentially the same result.

Cultures from the lungs and pale points in kidneys of *all three calves*—*i. e.*, Nos. 7, 8, and 9—were negative in so far as the development of acid-resisting bacilli were concerned.*

Calf No. 10.—On January 6, 1902, we injected into the left lung of Calf No. 10, 5 c.c. of a very thick suspension of Moeller's grass bacillus II. The suspension was made by mixing in 15 c.c. of bouillon the entire surface growth from three slanted glycerin-agar cultures that had been growing for seventy-two hours at 38° C. The animal was not apparently disturbed by the injection. It was killed March 8th—*i. e.*, sixty days after inoculation. When inoculated it weighed 185 pounds, when killed it weighed 201 pounds, making a gain of 16 pounds since the date of inoculation.

At *autopsy* there was a slight adhesion between the pleura and the chest wall at point of inoculation. This consisted of a slender thread or band of fibrous tissue. The pleura was not apparently thickened and the lung itself was not diseased. The surrounding tissues gave no macroscopic evidence of reaction.

There was nothing beyond that mentioned above worthy of note in the animal. In brief, its internal organs were normal.

Calf No. 11.—On the same date (January 6th) Calf 11 was inoculated in a similar manner with the same dose of the same suspension used on Calf 10.

* By reason of circumstances not under our control these autopsies were made in a high wind and practically in the open air, so that there developed in some of our cultures the ordinary saprophytic bacteria commonly found in the air. We did not, however, as stated above, find any bacteria in the tissues by microscopic examination, and feel justified, therefore, in regarding the growths in our culture tubes as accidental contaminations.

When inoculated it weighed 160 pounds, when killed it weighed 161 pounds, making a gain of 1 pound in sixty days.

Autopsy. On opening the great cavities nothing whatever of an abnormal nature was discovered. There was no adhesion of the inoculated lung to the thorax wall, and it was impossible to find the point at which the lung had been punctured by the needle.

The organs of this animal were so manifestly normal that it was not deemed necessary to preserve them for microscopic study.

Acid-resisting bacteria were not obtained in cultures made at the autopsies on either of the five preceding animals.

Calf No. 12.—Inoculated, March 22, 1902, with butter bacillus (Rabinowitsch). Fifteen c.c. of a freshly prepared suspension of butter bacillus (Rabinowitsch) were injected through the thoracic wall directly into the right lung of this animal. The suspension injected contained the entire surface growth from two well-developed glycerin-agar cultures of the organism.

At the time of inoculation the animal weighed 485 pounds, when killed, eighteen days later, it weighed 483 pounds, a loss of 2 pounds. The tuberculin test was made both before the animal was inoculated and immediately before it was killed, with negative results in both instances.

The animal was killed on April 9th. On opening the thorax there was found on the surface of the lung at the site of inoculation an irregular, tough, white patch, having much the appearance and consistency of fibrous tissue. It was irregularly oval, about 20 mm. in its greatest diameter, and about 5 mm. thick at its centre. From the centre it became thinner toward the periphery, and finally faded off into an irregular, ragged outer edge. On its under surface it was sharply, though irregularly, differentiated from the underlying lung by a reddish line of demarcation. The lung immediately beneath it appeared normal to the naked eye. At a little distance from this very superficial patch, and so located beneath the pleura as to be invisible from the surface, was another dense mass of whitish tissue of much the same general appearance as that found on the surface. On section this latter was found to be soft and cheesy at the centre, a characteristic not found in the more superficial deposit.

On microscopic examination of cover-slips made with scrapings from these deposits nothing of particular significance was discovered. They revealed only the presence of pus- and tissue-cells, blood-corpuscles and a great deal of granular detritus. No bacteria of any sort were certainly discovered.

Cultures from both points of disease revealed the presence of living butter bacilli (Rabinowitsch) in pure culture. There were no lesions of any of the other organs of this animal.

Microscopic examination of the diseased points showed the one more superficially located to be a mass of fibrin and cells with a certain amount of organization in progress at the part next to the lung. It contained no circumscribed foci of either caseation or suppuration, and neither bacilli nor actinomyces were seen, though, as stated, cultures from it revealed the presence of the organism with which the animal had been inoculated.

On similar study of the more deeply located nodule, which we take to be the point at which the bulk of the injected mass was deposited, there were found the characteristics of ordinary granulation tissue. It was marked by a number of larger and smaller foci of necrosis and suppuration, and scattered irregularly through it were a few typical giant cells. These latter were marked at their centre by the presence of smaller and larger clumps of acid-resisting bacteria. In some cases these bacteria stained poorly, in others well. Occasionally a giant cell was seen embedded in a more or less dense mass of polymorphonuclear leucocytes, while, again, such was not the case. Often the giant cells seemed to have been invaded by a few leucocytes which were entangled with the centrally located mass of bacteria. Throughout these sections acid-resisting bacteria in the form of short and long beaded rods and threads (see Fig. 1, *c*) sometimes irregularly scattered between the cells, sometimes massed together in very large, irregular clumps, were found in enormous numbers. No actinomyces and nothing to suggest them were encountered, neither was there anything about the animal to suggest tuberculosis.

Calf No. 13.—On March 22d, 15 c.c. of a suspension containing the entire surface growth from two well-developed slanted glycerin-agar cultures of butter bacillus (Rabinowitsch) were injected directly into the right lung of this animal.

At the time of inoculation it weighed 227 pounds; on the day it was killed, twenty-six days later, it weighed 263 pounds, being a gain of 36 pounds.

Tuberculin tests before inoculation, and again just before the animal was killed, gave negative results.

At autopsy, April 17th, it was impossible to certainly find the point of entrance of the needle into the lung. The lung was adherent to the chest wall in a number of places by new-formed tissue, and as this was most conspicuous at about the point where we suppose the needle had penetrated, we took it to be one of the results of the injection. There was nothing in the lung itself in this area that could properly be referred to the injection. In the lower lobe of this lung there was found an irregular, sharply circumscribed, fleshy area about 6 c.c. long, by 4 c.c. wide. This area extended well into the lung, was sharply defined, and was surrounded by what was apparently healthy lung tissue. The bronchi scattered throughout this area were filled with yellow muco-pus, and in many of them there were found, sometimes singly, sometimes massed together, tiny, actively motile, thread-like worms of a white color.

On microscopic examination of this lesion we found it to be the ordinary verminous pneumonia. No acid-resisting bacteria were found in it by either microscopic or cultural examination, though a certain number of colonies of bacilli and micrococci that were not resistant to acids appeared in the cultures. There was nothing about the lung that led us to believe the inoculation had had any serious effect. The other organs of the animal were to the naked eye normal. Cultures were negative in so far as acid-resisting bacteria are concerned.

Calf No. 14.—On March 22d, 12.5 c.c. of a suspension containing the entire surface growth from two well-developed slanted glycerin-agar cultures of Moeller's timothy hay bacillus were injected directly into the right lung of this animal.

At the time of injection the animal weighed 275 pounds; on the day it was killed, eighteen days later, it weighed 295 pounds, making a gain of 20 pounds.

Tuberculin tests before inoculation, and before the animal was killed, gave negative results.

At autopsy the only lesion found that could reasonably be referred to the inoculation was a tough, more or less raised area of about 8 mm. in diameter at the point where the needle entered the lung. This on microscopic examination proved to be only a thickening of the pleura with a few isolated areas of softening scattered through it. The remaining organs of this animal showed no pathological lesions. Cultures did not reveal the presence of acid-resisting bacteria.

Calf No. 15.—On March 22 the entire surface growth from two well-developed slanted glycerin-agar cultures of Moeller's timothy hay bacillus suspended in 12.5 c.c. bouillon was injected into the right lung of this animal through the thoracic wall.

At the time of inoculation the animal weighed 354 pounds; on the day it was killed, twenty-six days later, its weight was 384 pounds, making a gain of 30 pounds.

Tuberculin tests were negative both before inoculation and before the calf was killed.

At autopsy a few adhesions were found to have formed between the lung and the chest wall. Over the pleural surface of the lung, in the neighborhood of the point of inoculation, were numerous tiny transparent elevations having somewhat the appearance of deposits of fibrin. They were entirely superficial. Beyond these fibrin deposits we were unable to detect any disease whatever of the lung, notwithstanding the fact that macroscopic sections were made over a comparatively large portion of the lung in the neighborhood of where we presume the bacteria had been deposited.

The heart, liver, and spleen of this animal revealed no pathological lesions Upon the peritoneal surface of the intestines were numerous deposits of loosely adherent fibrin. On examining the peritoneal cavity closely a number of thread-like actively motile worms of about one and a half inch to two inches in length were found.

Microscopic examination of the deposits of fibrin on the surface of the lung showed them to consist of fibrin and cells. No bacteria were detected in them. There was nothing anywhere in this animal to suggest tuberculosis, or even to indicate that the injection had been the cause of a pathological lesion that in any way inconvenienced the animal. Cultures: no acid-resisting bacteria found.

The outcome of the foregoing experiments demonstrates, we believe, the incapacity of the organisms employed to cause in

calves lesions that might be mistaken for those of a tuberculous nature.

From both intravenous and intrapulmonary inoculation there was either no result at all or there occurred only local processes of an ordinary inflammatory character.

In the light of these results we believe that the presence of acid-resisting bacteria (other than tubercle bacilli) in dairy products may be interpreted as accidental contaminations from the surroundings under which the work is performed, and not as evidence of disease caused by these organisms in the animals from which the products are obtained.

THE BOTANICAL RELATION BETWEEN THE ACID-RESISTING BACTERIA AND BACILLUS TUBERCULOSIS. NOMENCLATURE, CLASSIFICATION, ETC.

In still other particulars we encountered both points of resemblance and of difference between these acid-resisting organisms and bacillus tuberculosis, notably in their modes of development in the affected tissues. As has been already beautifully demonstrated by Babes and Levaditi,[33] Friedrich,[34] Friedrich and Nösske,[35] and Schulze,[36] the growth of bacillus tuberculosis in the tissues of susceptible animals often assumes the character of typical actinomyces. This result has been obtained by the authors named through several methods of inoculation—by Babes and Levaditi through subdural in oculation of rabbits, by Friedrich and Nösske through intra-arterial injection of the same animal, and by Schulze through direct inoculation of the internal viscera as well as by the methods of the other investigators.

In our experiments we were able to confirm these observations by the simple method of intravenous injection (see Fig. 3). While we have observed the "ray fungus" form of growth of bacillus tuberculosis in a number of instances, it has not been by any means a common characteristic. We often found it necessary to examine many series of sections through tissues studded with tubercles before we encountered a single mycelium suggesting actinomyces. In the majority of cases the tubercles contained only irregularly clumped or diffusely scattered rods having all the well-known characteristics of bacillus tuberculosis.

Early in the course of our work with the acid-resisting group our attention was arrested by clusters of club-shaped bodies within the nodules in the tissues that in arrangement, general appearance, and type of tissue surrounding them bore many points of resemblance to actinomyces as one sees them in the actinomycotic tumor. At first they were encountered only occasionally in sections selected at random, but by systematic study of serial sections it soon became evident that this is the normal mode of development of these organisms in the tissues, and that in each nodule it is possible to detect, by that method of examination, the presence of one or more such mycelia. While the general character of these mycelia is the same for the three organisms studied by us—*i. e.*, all appear as more or less typical actinomyces, having a central mass of closely interwoven, fine, granular threads surrounded by a zone of radially arranged, elongated, club-shaped hyphæ—there are nevertheless interesting individual differences. For instance, the actinomyces developing from the butter bacillus (Rabinowitsch) and from the grass bacillus II. (Moeller), which do not differ materially from one another (see Fig. 4), are often (not always) much smaller, more delicate, and less numerous than are those from the timothy hay bacillus (Moeller), which are, as a rule, much larger and apparently more prone to "involution" changes. We say "involution changes," for this is the only expression that appears appropriate to some of the extraordinary appearances encountered in the actinomyces of this fungus. Now and again hyphæ of enormous proportions, relatively speaking, will be seen that are apparently split or creased in such a manner as to produce distinct spines or serrations along their edges and over the surfaces, causing at times the appearance of a miniature barley head or a tiny pine cone. (See Fig. 1, *d.*) The neighboring hyphæ may be of the ordinary club shape or may extend into the tissues as long, slender, ribbon-like projections. Sometimes they are homogeneous in structure, sometimes irregularly segmented. In several instances we were able, by appropriate methods of staining, to distinguish in the large club-shaped hyphæ a central thread or axis and an enveloping mass having different micro-chemical reactions (see Fig. 1, *e*), just as was done by Boström[37] in his exhaustive study of the ray fungus occurring in actinomycosis.

When in the diseased kidneys, the mycelia developing from the three organisms are much more alike than when in the lungs, though often in the kidneys the large, irregular timothy hay mycelia will be encountered. The lungs appear to offer conditions somewhat more favorable to the typical actinomyces development than do the kidneys. In one of our cases (mentioned above) the diseased areas in the lungs were marked by numerous isolated mycelia of an unusually beautiful appearance, consisting of long, thick, club-shaped, and ribbon-like hyphæ that radiated into the surrounding tissues from a small, central ring of short, oval, deeply staining bodies. (See Fig. 2.) At times these growing masses were surrounded by proliferating epithelioid cells in such a way as to suggest developing giant cells, while at other points they were completely surrounded by dense zones of polymorphonuclear leucocytes; between these extremes all grades of tissue reaction could be detected. The general character of these mycelia was so unusual as to lead us to suspect that they were possibly the growth of some fungus other than that with which the animal had been inoculated, and that they were, therefore, the result of an accidental infection; but their appearance in the typical nodules in the kidneys of this animal as well as in the lung, and the fact that the so-called timothy hay bacillus was obtained in pure culture from the affected areas, did not contribute to strengthen this opinion. However, a number of efforts were made to reproduce the picture; and while we have in three instances succeeded in doing so in part—sufficient to warrant the belief that our first case was not a mixed infection—we have only once duplicated the condition seen in our first case. In the majority of nodules the mycelia, instead of conforming in structure to those depicted in Fig. 2, were in general more like those shown in Fig. 5. Between these extremes all gradations from one to the other type could be encountered.

Occasionally the mycelia of the timothy hay bacillus were indistinguishable in size and configuration from those of grass bacillus II. and butter bacillus. In one case the growth of the butter bacillus was in the form of the larger mycelia often seen in the development of the timothy hay bacillus. Whether there is a direct connection between the type of mycelium and the character

and extent of the pathological lesion cannot with certainty be decided; but in our experience we have been impressed by the fact that the lesions resulting from the use of the timothy hay bacillus have, as a rule, been much more marked, more numerous, and more often encountered in the lungs than was the case with those caused by the other organisms used in these studies.

While a diffuse growth of these bacteria in the form of short rods, single and in irregular clumps, is now and then observed in the diseased tissues, it is far from constant. One may often examine a complete series of sections through a nodule or group of nodules without detecting any evidence of bacterial development except that given by the presence of the actinomyces. Whether these develop from a single cell or group of cells deposited in the tissues as a result of the method of inoculation we cannot say.

In contrast to this condition it is of interest to note that when large quantities of these organisms are injected directly into the tissues at a single point there is no development as actinomyces. They are seen instead as single rods and clumps of rods scattered irregularly throughout the affected area, just as is usually the case with bacillus tuberculosis in actively developing tubercles. In such cases the rods and threads are conspicuous for their granular structure, appearing often as long and short almost colorless tubes or sheaths, in which deeply stained round points are irregularly distributed. (See Fig. 1, *c*.)

It must be understood that our observations in connection with the actinomyces development of the acid-resisting bacteria are not unique. In an elaborate investigation of this subject Lubarsch[38] called attention to this mode of growth. He found, in so far as we can judge from his description and illustrations, practically the same conditions that have been noted by us, with the exception, perhaps, of the remarkable development depicted in Fig. 2. His method of investigation differed somewhat from ours, consisting in the main of intra-arterial injection and of direct inoculation of the internal viscera, as was done by Schulze (*loc. cit.*) in his work with bacillus tuberculosis. The organisms employed by Lubarsch, in addition to those used by us, were the bacillus of avian tuberculosis, "modified" bacillus tuberculosis, bacillus of fish tuberculosis, Moeller's mist bacillus, Petruschky's strep-

tothrix, streptothrix Eppinger, bacillus mallei, and bacillus diphtheriæ.

Actinomyces development was not observed in the case of bacillus mallei, bacillus diphtheriæ, and the streptothrix of Petruschky. With all the rest it was a common characteristic of their growth in the tissues.

In 1884 Petrone[39] expressed the belief that bacillus tuberculosis represents a phase of development of a parasite intermediate, morphologically, between the micromycetes and the schizomycetes. In 1888 Metschnikoff[40] remarked that what we are accustomed to see and designate "bacillus tuberculosis" is but a state in the life-history of a parasite of higher organization than the bacilli; and in 1893 we find Hueppe,[41] as a result of Fischel's[42] investigations, giving as his opinion that "the so-called tubercle bacilli are only the parasitic adaptation form of a fungus-like, pleomorphic microbe."

Through the investigations especially of Fischel (*loc. cit.*), Coppen-Jones,[43] Bruns,[44] Babes and Levaditi (*loc. cit.*), Friedrich and Nösske (*loc. cit.*), and Schulze (*loc. cit.*) the gist of these opinions—viz., that "bacillus" tuberculosis is a misnomer—has received sufficient support to warrant acceptation. It has been demonstrated that, in addition to the actinomyces-like development in the tissues of animals, the exciter of tuberculosis under artificial cultivation develops in the form of elongated, interwoven, branched threads—characteristics that we know are not peculiar to bacilli, strictly speaking. From the studies of a number of other investigators, especially Pettersson[45] and Moeller,[46] similar long, thread-like branching forms are to be seen in artificial cultures of some of the acid-resisting group.

From the evidence at hand, of which the foregoing citations represent only a small part, there can be little doubt of a botanical relationship between the so-called "bacillus" tuberculosis, the so-called acid-resisting "bacilli," the ray fungi, known to us in connection with actinomycosis of man and animals, and some of the so-called streptothrices concerned in the condition known as pseudotuberculosis. Nor can there be much difference of opinion as to the inaccuracy of the designation "bacillus" for these organisms. But how, then, shall they be generically designated? In

an elaborate thesis upon the ray fungi Lachner-Sandoval[47] presents a strong plea for their classification as actinomyces. He calls attention to the fact that the term "streptothrix," frequently used in recent times for some of the members of this group, has long been used by botanists to designate a class of fungi that have little or nothing in common with the organisms with which we are concerned, and that these latter organisms—*i. e.*, tubercle bacilli, acid-resisting bacilli, the so-called streptothrices of the medical bacteriologists, and the actinomyces of actinomycosis—cannot, therefore, be properly included with the streptothrices. Because of their many points of resemblance to the well-known actinomyces of actinomycosis in some cases, and because of the suggestive stellate (though less characteristic) growth in the tissues in other cases, he suggests the term "actinomyces" as the designation for the entire group — a suggestion that we are disposed to regard as appropriate to the case in point.

THE PRESENCE AND SIGNIFICANCE OF ACID-RESISTING BACTERIA IN BUTTER.

The detection of acid-resisting bacteria that may be mistaken for bacillus tuberculosis upon fodder and many cereals; in the soil and manure about barns and stables; in the secretions about the genitalia and udders of milk-producing animals, and in the milk and butter from such animals, evidently demands for them a special consideration by those who are responsible for the sanitary control of dairy industries.

Our knowledge of the occurrence of these organisms in dairy products dates from the observations of Petri[13] and of Rabinowitsch.[14]

Though bacillus tuberculosis had been demonstrated in milk and in butter by many competent observers, it was nevertheless somewhat disturbing to learn through the studies of Obermüller[48] that he had found them in all of fourteen samples of butter examined by him from a single source in Berlin. While commenting upon Obermüller's results, with the view of dissipating such apprehension as might be caused in the minds of readers, Petri[13] makes a preliminary announcement of results obtained by him in the

Imperial Health Bureau at Berlin. He found that in about 30 per cent. (!) of over a hundred samples of butter examined were tubercle bacilli certainly found, and that in about 60 per cent. of the samples there was present an organism which might be readily confounded with bacillus tuberculosis. In his completed contribution it appears, to be precise, that 102 samples of butter were subjected to careful study by both microscopic and inoculation methods; that of these 32.3 per cent. contained genuine tubercle bacilli capable of causing tuberculosis when inoculated into guinea-pigs, while in 52.9 per cent. of them was a "new" organism ("stäbchen"), which in stained preparations bore an extraordinary resemblance to bacillus tuberculosis, and which when injected with butter into animals caused lesions that were remarkably like those of genuine tuberculosis. In 16.7 per cent. of the samples genuine tubercle bacilli were found alone; in 37.2 per cent. only the "new" bacterium was present, while in 15.7 per cent. the two organisms were found together.

Of sixty-four samples of milk examined 14 per cent. contained genuine tubercle bacilli, and 6.3 per cent. the "new" bacterium.

In the case of both milk and butter the results given were reached through animal inoculation, 408 guinea-pigs having been inoculated with the butter and 478 with the milk.

He expresses the opinion, in the light of these results, that the simple microscopic examination of butter and milk with the view of identifying bacillus tuberculosis by its micro-chemical staining reaction is untrustworthy.

Almost coincidently with Petri's preliminary announcement appeared a contribution from Rabinowitsch[14] which has also attracted a great deal of attention as well as done much to further elucidate the subject. In this paper she states that Koch had long suspected the existence in dairy products of bacteria that might be and that probably had been mistaken for true tubercle bacilli. It was this thought that led him to suggest her investigation. Under precautions against which no objections could be raised Rabinowitsch examined by microscopic, cultural, and inoculation methods thirty samples of butter purchased in the open markets of Berlin and fifty in Philadelphia. In twenty-three samples (ten in Berlin and thirteen in Philadelphia)—*i. e.*, 28.7

per cent. of the total number examined—acid-resisting bacteria were found which, in morphology and staining reactions, more or less closely resembled bacillus tuberculosis. In their cultural peculiarities these organisms were readily distinguishable from bacillus tuberculosis, but when injected with butter into the peritoneum of guinea-pigs they possessed the property of causing nodular lesions that both to the naked eye and by microscopic examination had some of the characteristics of true tubercles. In this investigation she failed to find tubercle bacilli in a single one of the eighty samples of butter examined; but in a subsequent study of butters obtained from nineteen different places in Berlin the samples repeatedly obtained from one source were always found to contain them, while those from the remaining eighteen sources were regularly free from them.

As the place from which the tuberculous samples were regularly obtained was one of the best-known butter shops in Berlin, she suspects that the discrepancy between her results and those of some of the other investigators, who encountered tubercle bacilli much more frequently in butter, may be in part explained by their having obtained their samples from the shop from which she regularly secured the tuberculous butter.

The investigations of Herbert,[17] conducted in Baumgarten's laboratory at about the same time that Petri and Rabinowitsch were engaged in their studies, are of no less interest and importance than those of Petri and of Rabinowitsch. He examined 126 samples of butter from various sources for the presence of tubercle bacilli, and failed to detect them in a single instance. In only five per cent. of one hundred samples from various sources in Würtemberg were acid-resisting "pseudotubercle" bacilli present, while in ten out of twenty (50 per cent.) of the Berlin samples and four out of five (80 per cent.) samples from Munich they were found.

While the works just cited by no means deny the occasional occurrence of tubercle bacilli in butter, they nevertheless indicate their comparative infrequency in samples selected at random. On the other hand, the studies of Rabinowitsch leave no doubt, as had already been emphasized by Obermüller, that butter from particular sources may now and again be encountered in every sample

of which the living virus of tuberculosis may be regularly demonstrated. For our present purpose it is also important to note that though tubercle bacilli were seldom encountered, except in Petri's studies, the acid-resisting, confusing species, though far from regular in their occurrence or distribution, were much more common, having been encountered, as said, by Petri in about 53 per cent. of samples, by Rabinowitsch in about 23 per cent., and by Herbert in from 5 per cent. to 80 per cent., according to the locality from which the samples came.

With the view of acquainting ourselves with the acid-resisting bacteria under their presumably saprophytic existence and of securing material with which to pursue our work, we conducted a series of studies upon butters purchased in Philadelphia.

Fifty samples in all were examined. Thirty-five of these were butters from public creameries, fifteen from private dairies.

Of the fifty samples examined seventeen could properly be designated as good butter, sixteen as medium, and seventeen as markedly poor butter.

Our methods of experimentation were as follows: The samples of butter were melted at from 37° C. to 39° C., and the injections into animals were made as follows:

From one sample 1 c.c. of the whole (mixed) melted butter was injected into the peritoneal cavity of each of four guinea-pigs.

From fourteen samples 1 c.c. of the sediment that collects in the melted butter on standing was injected into the peritoneal cavity of each of twenty-eight guinea-pigs, two pigs being used for each sample.

From thirty-five samples a sediment was obtained by centrifugalization after the plan suggested by Obermüller, and of this sediment from 1 to 1.8 c.c. was injected into the peritoneal cavity of guinea-pigs. One hundred and four animals were used in the investigation.

For each of forty-eight of the samples of butter two animals were used, while for each of the remaining two samples four animals each were used.

Of the 104 animals thus treated thirty-one died of general infection in from two to nineteen days after injection. One died in thirty-four days after the injection, and its peritoneum was

marked by nodular growths from which acid-resisting bacteria were isolated. In the loose tissues at the angle between each kidney and its adrenal body, and adherent to the capsule of the kidney, was an abscess of about 3 mm. in diameter. By both microscopic and cultural methods acid-resisting bacteria were demonstrated in these abscesses.

Five of the remaining seventy-two animals that were killed in from forty-three to sixty-eight days after inoculation showed the presence of nodular growths in the peritoneum in which acid-resisting bacteria were detected by microscopic examination and from which they were isolated in pure cultures; while of the balance, sixty-seven in all, sixty-six were killed in from thirty-one to sixty-nine days after the inoculation, and found to be devoid of lesions that could have been mistaken for tubercles or that would have been likely to have caused the death of the animals; and one died thirty-eight days after inoculation, the autopsy revealing dense adhesions of the intestines to one another and to the liver and gall-bladder. No nodules of any sort were detected. By both microscopic and cultural methods of examination the peritoneum was found to be sterile.

The nodules found in the peritoneum of the animals from which acid-resisting bacteria were cultivated may fairly be said to have suggested tubercles to the naked eye only remotely. They were nodular and were isolated, it is true; but they were of a yellowish or whitish appearance, were less sharply circumscribed than tubercles, were confined to the peritoneum, showing little or no tendency to invade the deeper structures of the organs or to metastasis throughout the body, and were generally devoid of the clear, pearly appearance seen in genuine young tubercles. On microscopic examination they were all so characterized by the invasion of leucocytes and by the absence of caseation, giant-cell formation, or the necroses typical of tuberculosis that we could see no reasonable excuse for mistaking them for tubercles. In two of these cases, in addition to the tiny nodules, small, unmistakable abscesses were present; in one of these cases there was a small, circumscribed focus of suppuration in the loose tissues about the right kidney, and in the other there was a similar abscess in the left testicle.

Six of the ten animals that had been inoculated with the five samples of butter in which acid-resisting bacteria were detected presented the nodular lesions noted above. Of the remaining four animals inoculated from these samples negative results were obtained in one, and three died of acute infection.

Without entering into details it will suffice to say that throughout our experiments the deaths due to acute general infection were referable to the activities of staphylococcus pyogenes aureus, bacilli of the colon and proteus groups, and to streptococcus pyogenes. In the case of one sample of butter the two animals inoculated with it were killed fifty-two days after the intraperitoneal injection, and the only organisms found in their tissues were yeast cells. There were no suspicious nodules detected. In the majority of samples examined by us yeast cells were found by direct microscopic examination of the sediment.

In four of the five samples of butter that caused nodular lesions of the peritoneum acid-resisting bacteria were found by microscopic examination of the sediment. In one they were missed. In another sample acid-resisting bacteria were detected microscopically in the sediment, but of four animals inoculated from this sample three died of acute infection; while the remaining one, killed forty days after inoculation, was devoid of pathological lesions.

In none of the fifty samples of butter examined was the presence of genuine tubercle bacilli demonstrated by intraperitoneal inoculation of guinea-pigs, though it must be remembernd that a fairly large proportion of the animals—*i. e.*, 29.8 per cent.—died of acute infections; some of them before tubercle bacilli that might possibly have been present could have exhibited their specific disease-producing properties.

Three of the five samples of butter in which acid-resisting bacteria were detected were from private dairies, while two were from public creameries.

In the selection of our samples for investigation care was taken to secure them from as many different sources as possible. They were purchased in the open market, sometimes from retailers, at others from the wholesale dealers. They were all purchased in different parts of the city, and, so far as we can say, no two samples were made at the same place.

In brief, of fifty samples of butter from various sources examined by us five samples, or 10 per cent., contained acid-resisting bacteria that simulated bacillus tuberculosis in some of their staining reactions; that suggested that organism by certain morphological peculiarities; and that were capable of causing nodular lesions when injected with butter into the peritoneum of the guinea-pig.

Genuine tubercle bacilli were discovered in none of them.

Organisms capable of causing acute peritonitis or general infection were present in twenty-one of them.

From one of the five samples containing acid-resisting bacteria two varieties of those organisms, easily distinguished from one another, were isolated. In one of the samples the acid-resisting organism, while being a rod with resistance to decolorization by weak acids, was only occasionally suggestive of bacillus tuberculosis in morphology. In culture it was unlike any of the group that we have had an opportunity to study, developing on glycerin-agar as a moist, slimy layer of an orange color that remains throughout of a distinctly mucoid consistency. At no time does it present the dry, granular, wrinkled appearance of the type members of this group.

Only four of the cultures isolated by us possess the group-characteristics common to such typical members as the grass bacillus II. and timothy bacillus of Moeller and the butter bacilli of Petri and of Rabinowitsch.

We have not studied the cultures isolated by us in all details, since for the purposes of this paper it seemed sufficient to determine the possession by them of such characteristics as would justify their inclusion in this group. We have as yet made no direct effort to identify them with the several varieties described by other observers.

The results of intravenous inoculation of rabbits with large doses of pure cultures of three of the organisms isolated by us were negative after thirty to thirty-three days.

The microscopic appearance of the acid-resisting bacteria in the samples of butter in which we found them was (when they were stained by the Gabbet method or by the Koch-Ehrlich method, and decolorized by 5 per cent. sulphuric acid in water) sufficiently suggestive of bacillus tuberculosis to render the differ-

entiation from that organism by the microscope a matter of difficulty if not of impossibility.

CONCLUSIONS.

1. That the majority of the acid-resisting bacteria may be distinguished from true tubercle bacilli by their inability to resist decolorization by a 30 per cent. solution of nitric acid in water.

2. That some of the acid-resisting bacteria are capable of causing in rabbits and guinea-pigs nodular lesions suggestive of tubercles; that these lesions, while often very like tubercles in their histological structure, may nevertheless usually be distinguished from them by the following peculiarities:

(*a*) When occurring as a result of intravenous inoculation they are always seen in the kidneys, only occasionally in the lungs, and practically not at all in the other organs.

(*b*) They constitute a localized lesion, having no tendency to dissemination, metastasis, or progressive destruction of tissue by caseation.

(*c*) They tend to terminate in suppuration or organization rather than in progressive caseation, as is the case with true tubercles.

(*d*) They are more commonly and conspicuously marked by the actinomyces type of development of the organisms than is the case with true tubercles, and these actinomyces are less resistant to decolorization by strong acid solutions than are those occasionally seen in tubercles.

3. That by subcutaneous, intravenous and intrapulmonary inoculation of hogs (4) and calves (15) the typical members of the acid-resisting group are incapable of causing lesions in any way suggestive of those resulting from similar inoculations of the same animals with true tubercle bacilli.

4. That though occasionally present in dairy products, they are to be regarded as of no significance, etiologically speaking, but may be considered as accidental contaminations from the surroundings and not as evidence of disease in the animals.

5. That the designation "bacillus" as applied to this group of bacteria and to the exciter of tuberculosis is a misnomer; they are more correctly classified as actinomyces.

In closing this contribution we wish to express our obligation and thanks to Dr. Alfred Moeller, of Belzig; Dr. Lydia Rabinowitsch-Kempner, of Berlin; Professor Hueppe, of Prague; Dr. Norman McL. Harris, of Baltimore, and Drs. Ravenel and Kneass, of Philadelphia, for their courtesy in sending to us cultures with which to carry out our investigations.

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DISCUSSION.

DR. FLEXNER: I had the privilege of going over a number of Dr. Abbott's specimens, and there can be no doubt that the lesions produced by this group of organisms are not true tubercles. They consist of epithelioid cells, lymphatic cells, and not infrequent giant cells, but the types of the latter are those generally regarded as foreign-body giant cells, and not the typical ones of tuberculosis. Then the whole lesion taken together reminds one of granulation tissue, and such giant cells are often found there. A few years ago, when we were much excited over the pathogenicity of blastomycetes, I studied that question somewhat, and I should say that the lesions of this group are very similar to those produced by the yeasts.

DR. COHEN: I should like to ask Dr. Abbott whether he found any differences in the reactions of different classes or species of animals.

DR. MELTZER: I would like Dr. Abbott to tell us something more about the methods of recognizing these organisms, and particularly to say something about the alcohol methods of staining. It is an important practical question, because we meet a number of patients who show no particular lesion but the presence of tubercle bacilli in the sputum. A case was recently reported of a man who had for many years been considered as tuberculous, but on examination by Dr. Leiden he pronounced against that after a test in which he decolorized the organisms with alcohol.

DR. ABBOTT: In reply to Dr. Cohen, it is interesting to note that where pure cultures of the organisms only are employed the one certain way of getting results is to select small animals, the rabbit or guinea-pig, and make the injections into the circulation; if one inject beneath the skin even large quantities of pure culture the results are often negative or at most insignificant.

As to Dr. Meltzer's question, I cannot say that we have studied all the various methods of differentiation. Early in our work it became evident that the old method of staining and decolorizing by nitric acid was so satisfactory for differential purposes that we ceased to experiment with other stains.

EXPLANATION OF ILLUSTRATIONS.

FIG. 1.—Morphological variations.

(*a*) Pure culture on agar-agar, showing bacillary forms homogeneously stained.

(*b*) Pure culture on agar-agar, showing bacillary forms in an extremely granular condition.

(*c*) Long and short markedly granular forms sometimes seen in the tissues.

(*d*) Involution forms occasionally seen in the actinomyces developing in the tissues after intravenous injection of the timothy hay bacillus.

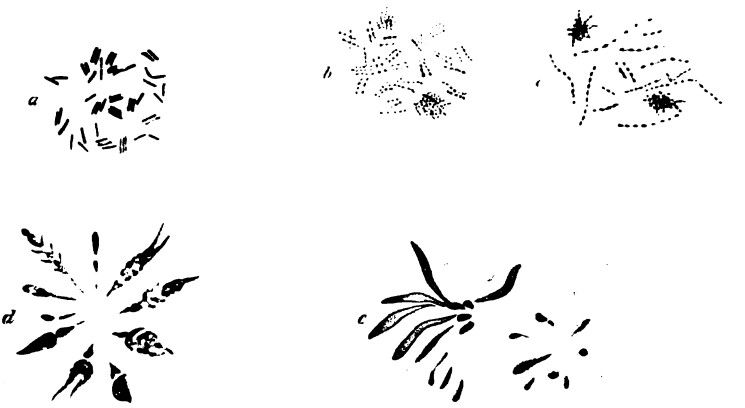
(*e*) Showing composite nature of the large club-shaped hyphæ from the timothy hay mycelia. Stained by the method suggested by Mallory for the actinomycosis fungus ("method No. 1").

FIG. 2.—Unusual type of development of the timothy hay bacillus in the lung of rabbit. Tissue stained with Ehrlich's acid hæmatoxylin; mycelia stained by the safranin method of Babes.

FIG. 3.—Actinomyces development of bacillus tuberculosis. Tubercle in lung of rabbit thirty days after intravenous injection of pure culture of bacillus tuberculosis. Partly decolorized with acid alcohol after staining in carbol-fuchsin.

FIG. 4.—Actinomyces type of development of butter bacillus Rabinowitsch. Kidney of rabbit after intravenous injection of pure culture. Staining as per Fig. 2.

FIG. 5.—Actinomyces type of development of timothy hay bacillus in lung of rabbit after intravenous injection of pure culture. Staining as per Fig. 2.



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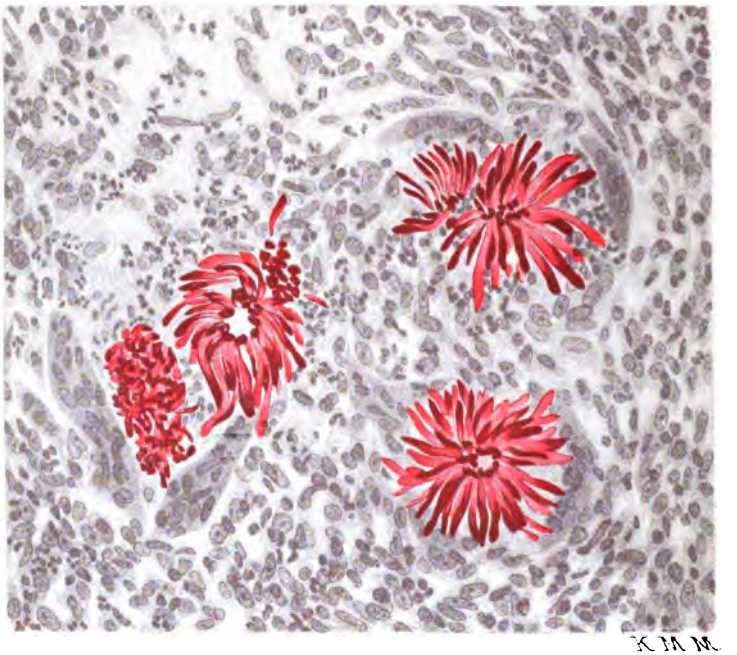
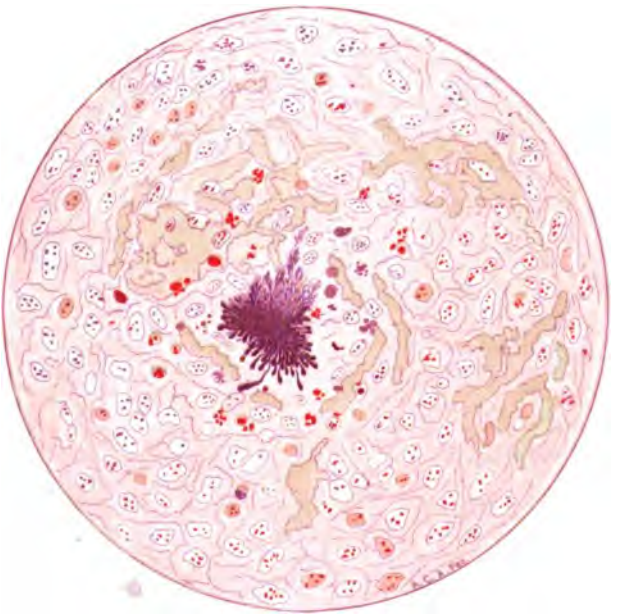


Fig. 2.



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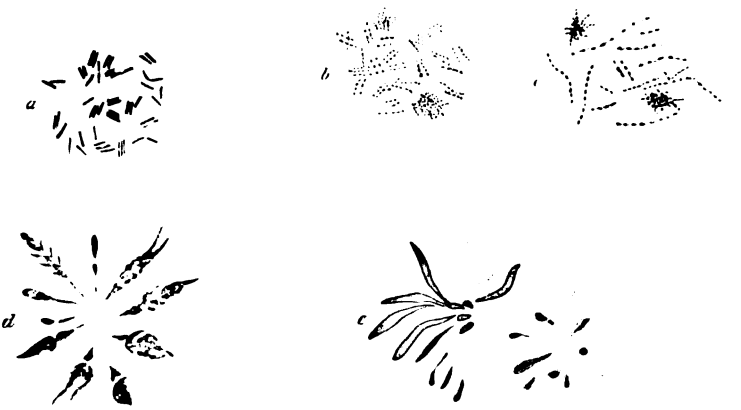

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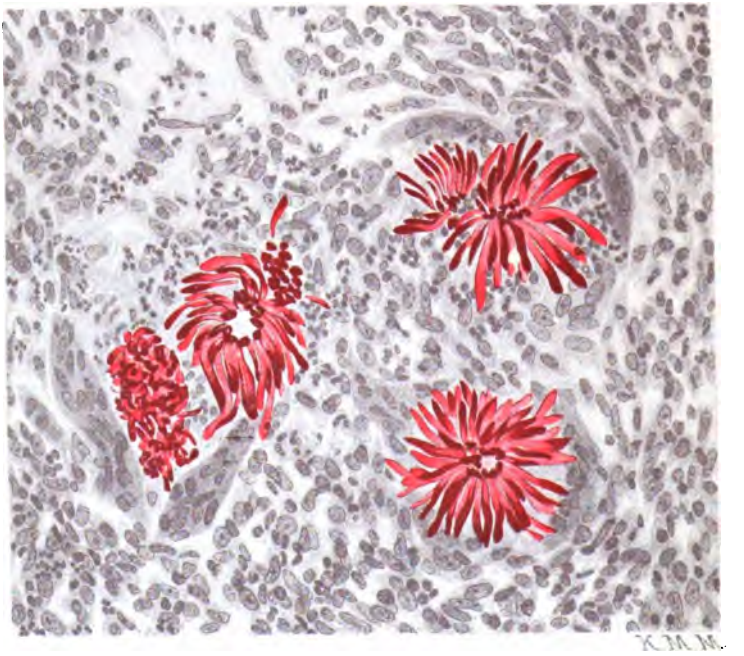

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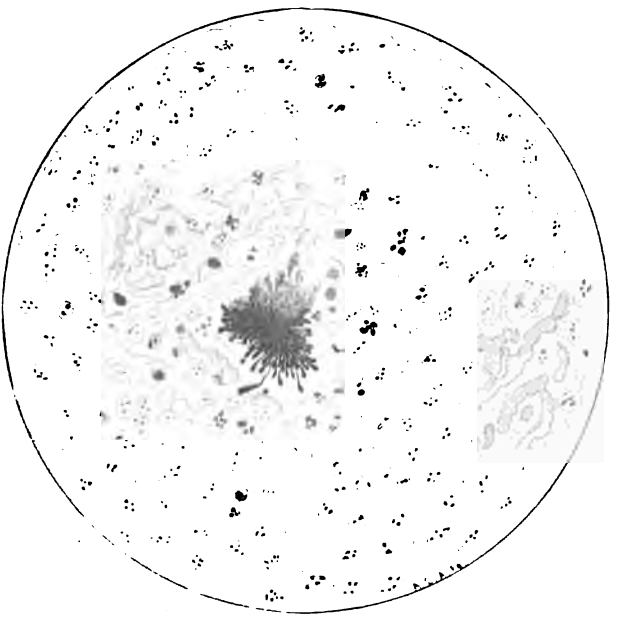

Fig. 3.

PANCREATIC LITHIASIS, WITH REPORT OF A CASE.

By FRANCIS P. KINNICUTT, M.D.,
OF NEW YORK CITY.

THE scanty literature of pancreatic lithiasis, as well as general pathologic records, give little exact information on the frequency with which pancreatic concretions are found in the gland after death.

Decisive evidence *intra vitam* of the existence of pancreatic lithiasis by the recovery of the characteristic concretions from the stools is exceedingly rare.

The literature contains the records of only six cases in which either a positive diagnosis of pancreatic lithiasis was made or such a pathologic process was suspected during life. The cases are so rare that a brief abstract of them is permissible.

CASE I. (Capparelli's[1]).—An abscess developed in the epigastric region, and through a fistulous opening which was established and persisted for six years over one hundred small pancreatic calculi were passed from time to time. The fistula finally closed, and a month later the existence of a glycosuria was discovered, which, it is stated, yielded to treatment. Capparelli believed that an interstitial pancreatitis was produced by the inflammatory affection, which in turn was the cause of the glycosuria.

CASE II. (Lancereaux's[2]).—Eight years before the patient, a female, came under observation there had been several attacks of sharp abdominal colic, and the stools were stated to have been "fatty." No further disturbance of the health occurred until eighteen months before admission to the hospital, when symptoms of glycosuria developed, and the patient finally was admitted, presenting all the symptoms of advanced diabetes mellitus. The existence of a pancreatic lithiasis was regarded as probable from the development of a diabetes subsequent to the attacks of abdominal colic.

At autopsy the body of the pancreas was found to be reduced to a simple fibrous cord and occupied almost exclusively by the pancreatic duct. The head was better preserved. The canal of Wirsung opened into the duodenum 2 cm. above the ampulla, and its orifice was occluded by a calculus of the size of a small pea.

CASE III. (Leichtenstern's[3]).—Following a severe attack of what was believed to be biliary colic without jaundice, three concretions, varying in size from a millet-seed to a pea, were recovered from the stools. Chemical analysis showed that these were composed of the carbonate of lime without traces of bile pigment or cholesterin.

CASE IV. (Leichtenstern's[3]).—The patient had suffered during a period of two years from periodic and exceedingly severe attacks of abdominal colic, with vomiting. On one occasion icterus had been present. A diagnosis of cholelithiasis was made by several physicians, a cholecystotomy was performed, but no biliary calculi were found. The attacks of pain continued and made life unendurable. A second laparotomy was done, and, no biliary calculi being discovered, the pancreas was explored. It was found to be enlarged. At autopsy, on section, the pancreas was found to be riddled with small abscesses, varying in size from a millet-seed to a pea, in which, as well as in the ducts, there were numerous pancreatic concretions. The sequence of events was evidently pancreatic lithiasis, secondary infection, suppurative pancreatitis.

CASE V. (Lichtheim's[4]).—A definite and correct diagnosis was made during life in this case. The patient, a male, thirty-six years old, gave a history of attacks of severe pain in the epigastric region, accompanied by vomiting and fever, beginning fourteen years before admission to the hospital, and recurring at intervals during a period of six years. Following this period he remained well until one year before admission, when he began to suffer from diarrhea, sudden in onset and without apparent cause. There was an absence of pain and fever; appetite and thirst were increased; emaciation and weakness progressively increased.

On admission to hospital physical examination was negative, except as to the lungs, which showed evidence of tuberculosis. The urine contained a large amount of sugar, which disappeared after two weeks of strict diet, and remained absent. The patient died three weeks later as a result of exhaustion from the diarrhea and the tuberculous infection.

The diagnosis of pancreatic lithiasis was made by Lichtheim previous to the death of the patient. This diagnosis was based upon the attacks of severe colic, with fever and vomiting, in the previous history of the patient. These symptoms were clearly those of calculi. Gallstones were excluded by the absence of signs of biliary stagnation, notwithstanding the long duration of the attacks. Renal calculi were excluded by the site of the pain and the absence of urinary signs.

In consideration of the subsequent diabetes Lichtheim believed the attacks of colic to have had their origin in the pancreas, and assumed them to have been due to calculi, and the resultant diabetes to pancreatic cirrhosis. The diarrhea also was attributed to the pancreas, through disturbance of intestinal digestion from failure of pancreatic secretion. Intestinal tuberculosis had been excluded by the absence of bacilli in the stools.

"Typical fatty stools" were not observed, although fats were administered experimentally. The abundant muscle fibers found in the stools were con-

sidered to be of doubtful diagnostic value, through the restriction of the patient to a strict meat diet and in the presence of a free diarrhea.

Autopsy showed marked dilatation of the main pancreatic duct, which was filled with a grayish fluid, in which were three large and many small mortar-like concretions.

Dilatation extended to the lesser ducts and as far as the cauda. The substance of the pancreas consisted chiefly of firm connective tissue, in which, however, small lobules of glandular tissue were distinctly visible.

Lichtheim believes his case to be the first in which the significance of the symptoms was appreciated during life, with the exception of Capparelli's. He quotes Friedreich, who asserts the impossibility of differentiating between biliary and pancreatic colic, inasmuch as the pancreatic calculi must simultaneously exert compression on the common bile-duct when they occlude the pancreatic duct. Lichtheim points out that his case demonstrates that this does not invariably occur, and that under some conditions the differential diagnosis can be made. In Case VII. of this series occlusion of the common bile-duct did not occur.

CASE VI. (Minnich's[5]).—A correct diagnosis of pancreatic lithiasis *intra vitam* was made in this case also. The patient, a male, aged sixty-eight years, gave a history of prolonged attacks of biliary colic, demonstrated to be such by the recovery of typical gallstones from the stools on two occasions (twenty-eight and eighteen years, respectively) before admission to the hospital. Two slight attacks of a similar nature, apparently, occurred six months before admission. A month before admission there was a slight attack of epigastric pain, lasting a fortnight, followed by a severe attack of diarrhea, without pain.

On admission to the hospital the patient stated that he had suffered from a severe pain located in the left epigastric region since the previous day. The sclera presented a slightly yellowish tinge, but the skin was not discolored. Careful abdominal palpation gave entirely negative results.

The patient described his pains as follows: "There is at first a dull, oppressive, constricting sensation in the epigastrium and under the left costal arch within the nipple line, which at times impels him to take deep inspirations and at times causes him to press upon the painful region with his hand. The pains soon increase until they become true paroxysms, and become more and more localized at a point close under the left costal arch and inside of the nipple line. At the height of the attack the pain radiates from this point along the costal arch to the spine and spreads with severity up under the left shoulder-blade. As the pain subsides it retreats to the point described under the left costal arch, the area of which could be covered by a five-franc piece."

A careful examination of this area as well as of the other painful regions elicited nothing positive except a slight sensitiveness on deep palpation over the former. The attack ceased suddenly after two hours, and the patient felt perfectly well and was decidedly hungry. An examination of the urine passed immediately after the attack showed it to be free from albumin, sugar, and biliary pigment. Subsequent attacks occurred almost daily, and were variable in severity.

The stools were carefully searched during twelve consecutive days, with the result of finding concretions varying in size from that of a cherry-pit to irregular detritus. The concretions were tough, semisolid in consistence. They were fractured by the pressure of the finger, but not reduced to powder. They were too coherent to be amalgamated by pressure. Nearly smooth superficially, gray externally, and of a dull-white luster on section, resembling fruit-seed. No stratification or nucleus discerned. Microscopically, amorphous. Chemically, easily soluble in chloroform, giving a turbid fluid. On heating in a tube a thick smoke of strong aromatic odor was given off; yellowish tinged water condensed in the cooler portion, and a residue of carbonate and phosphate of lime was obtained.

The attacks gradually abated in severity and frequency. After a time concretions were no longer detected. The patient recovered his usual health at the end of a month. No sugar or albumin was detected at any time in the urine. There was no loss of weight, and there was no fever at any period.

I am able to present to the Association the clinical report of an additional case in which characteristic pancreatic calculi were recovered from the stools.

CASE VII.—Mrs. H., forty-two years of age. The family history is unimportant. The personal history is that in 1888 the patient suffered from a slight attack of the following nature: A sudden onset of pain, first felt in the back between the shoulders, thence gradually extending from the point of origin around the right side along the lower intercostal spaces, accompanied with nausea and vomiting uncontrollable for a number of hours. Gradual subsidence of all the symptoms without medication; a slight diarrhea, accompanied and followed the attack; duration of the attack eight or nine hours. Similar though severer attacks in August and May, 1897 and 1898, respectively—three altogether. None of the attacks described were accompanied by jaundice, and biliary calculi were not found in the stools. They were believed to be due to a cholelithiasis. No further attack until January, 1901, when one of an exceedingly severe character occurred. The pain was first felt between the shoulder-blades, thence extended through and not around the body into the epigastrium, and became localized rather to the right of the median line. Vomiting occurred only once; the pain was very acute, necessitating the use of large hypodermic injections of morphin, which afforded only partial relief. The bowels were constipated throughout

the attack, which was of three days' duration. More or less abdominal pain and much general abdominal sensitiveness were experienced for four weeks subsequent to the acute attack. Jaundice was not present at any period. On the sixth day from the beginning of the attack six small stones the size of a pea were passed by the bowel. The patient had been under the care of a New York physician, and was seen in consultation by Dr. Janeway. It was believed that she was suffering from biliary colic. Dr. Janeway's attention was attracted by the appearance of the concretions passed, and he secured them for chemical analysis. Four of the concretions were analyzed, and were found to consist of the carbonate and phosphate of lime, without traces of cholesterin or bile pigment, indicating their origin in the pancreatic ducts. A similar though less severe attack occurred three weeks later, and others in August, October, and November, 1901—five in all The attack in August occurred in Berlin, under the observation of Prof. Leyden's assistant, Dr. Wohlgemuth. A small fragment of a calculus and considerable detritus were recovered from the stools, and the patient states that their origin in the pancreas was asserted. The attack in November occurred in San Francisco, under the observation of Dr. McMonagle. Although no concretions were recovered from the feces, considerable detritus was obtained, which was found to be composed of the carbonate and phosphate of lime.

The patient first came under my observation on December 25, 1901, on her arrival from San Francisco, whence she had come for further medical advice.

One of the concretions passed by the bowel in the attack of January, 1901, was given to me for examination. A chemical analysis showed it to be identical in its composition with those analyzed by Dr. Janeway. The only concretion unanalyzed, and which is identical in its appearance with the others, I am able to show you. It weighs 7 centigrams, with diameters of 5.8 x 5.9 x 6.2 mm. It will be seen that its surface is slightly rough, with several deep grooves. The material of which the surface is composed is found by chemical analysis to be phosphate of lime without admixture of the carbonate. The whole stone is very friable. The patient stated that she had suffered almost continuously from intestinal indigestion and from epigastric discomfort since the last attack in November, and for the previous ten days there had been more or less continuous epigastric pain. She had also lost much in weight. Careful physical examination only elicited the signs of a moderate degree of displacement of the right kidney and distinct sensitiveness over the region of the gall-bladder. Its palpability was considered doubtful. On the following day an acute attack occurred. As in all previous attacks, the pain began in the middle of the back between the shoulder-blades, and extended through and not around the body, locating itself in the central epigastric region. There was accompanying nausea and vomiting. There were recurring paroxysms for forty-eight hours, when they ceased. The urine, even at the beginning of the attack, contained traces of bile pigment, but no glucose. Later a slight degree of jaundice was appreciable, which speedily disappeared.

Similar attacks occurred on January 13th and 18th, except that they were preceded by a sharp chill, followed by a rise of temperature to 104°, which was again normal at the end of eight hours. No jaundice accompanied these attacks. All the stools from the beginning were passed through a very fine sieve, but no concretions were recovered. Following the last attack a few white particles were recovered which, on chemical analysis, were found to consist of calcium soaps (calcium oxide, 7.9 per cent.; higher fatty acids, including moisture and foreign matter adherent, 92.1 per cent.).

Finally, two very severe attacks accompanied by jaundice occurred during the subsequent three weeks, and a calculus was recovered from the stools on each occasion. Their composition was found to be nearly identical. Chemical analysis of the central portion of one concretion gave 92.44 per cent. cholesterin and 7.55 per cent. moisure and bile, indicating its biliary origin. It is of interest to note that cultures of the central portion gave no growth.

There has been an absence of attacks since those last described, but there has been continuous epigastric discomfort and pain located in the central portion of the back.

Throughout the period of observation very frequent examinations of the urine have never revealed any trace of sugar.

Immediately subsequent to the attack of January 18th, the color of the feces indicating a free flow of bile into the bowel, an investigation was undertaken to determine the utilization of the fat of a known diet. The report of the details of the investigation is appended: 101.4 grams of fat were ingested during a period of forty-eight hours, and 11.1 grams were recovered from the feces, indicating a normal absorption.

On the other hand, the composition of the fat was: neutral fat, 42.6 per cent.; fatty acids, free, 19.2 per cent.; fatty acids, soaps, 38.2 per cent. According to Mueller,[6] 42.6 per cent. of neutral fat in the feces is much above the normal, and indicates an at least *diminished* flow of pancreatic secretion into the intestine.

The clinical history of the case presents many points of interest. The decisive evidence *intra vitam* of the existence of a pancreatic lithiasis and its alternation with a cholelithiasis are of especial interest. In view of the origin of biliary calculi in many instances in an infection of the gall-bladder, an origin of pancreatic calculi in an infection of the ducts would seem not improbable. The clinical history of the patient in the past and her present symptoms suggest an explanation of the deficient utilization of the ingested fat. A pancreatic lithiasis *preceded* the cholelithiasis. It would seem probable that it also *coexisted* with the cholelithiasis, and that it is still present, with partial occlusion of the pancreatic duct or ducts.

A study of the cases related indicates the difficulties of a differential diagnosis between pancreatic lithiasis and cholelithiasis in the absence of concretions in the stools. As Oser[7] remarks, almost as great difficulties obtain in the diagnosis of pancreatic disease in gen-

eral, due to the fact that only extensive destructive processes in the organ or the closure of both ducts produce characteristic symptoms. Coincident disease of neighboring organs, either a cause or a result of pancreatic disease, may produce symptoms more distinct and impressive than those of the latter. A biliary calculus may lead to a chronic pancreatitis through its obstruction in part or wholly to the outflow of the pancreatic secretion into the intestine, and in itself produce symptoms which mask those of the pancreatitis.

It will be of interest to consider the symptoms which have been described by various authorities as those of occlusion of the pancreatic ducts.

1. None of the subjective symptoms, such as nausea, vomiting, diarrhea, can be regarded as characteristic. The belief that a ptyalism of varying degree accompanies a deficient secretion of the pancreatic juice, either through occlusion of the ducts or disease of the gland, is not borne out by clinical experience.

2. Clinical evidence indicates that the pain present in pancreatic lithiasis probably differs neither in kind nor location from that of cholelithiasis. In the single case of Minnich the location of the pain along the left costal arch was possibly suggestive. On the other hand, in my own case, the patient was very positive that the pain in the attacks preceding the passage of the pancreatic concretions and in the attack in which the concretions were recovered, began either along the right costal arch or in the back, finally becoming localized to the right of the median line.

3. The presence of an unusual number of undigested striated muscle fibers in the stools cannot be regarded as a basis for positive diagnostic conclusions. Abnormal quantities of muscle fibers are often passed in other disturbances of the intestinal digestion. In any free diarrhea this may occur.

4. *Fatty Stools.* An abnormal amount of fat in the feces is by no means a constant or even frequent symptom of pancreatic disease. In 330 cases collected by Ancelet[8] it was found only twenty-eight times. When present it is often due to the existence of jaundice in which the absorption of fat is enormously diminished (as much as three-fourths of the fat ingested may be returned in the stools, one-tenth being the maximum normal amount—Mueller[6]), or to various affections of the absorbents of the intestines. In Case VII. the *absorption* of fat was

found to be normal. A deficient splitting-up of the ingested fat into fatty acids and soaps, on the other hand, apparently is a symptom of great value in the diagnosis of occlusion of the pancreatic ducts from any cause. Mueller's[6] investigations, corroborated by Weintraud[9] and Katz,[10] show that normally 75.8 per cent. of the fat contained in the feces is split up, and appears, not in the form of neutral fat, but of fatty acids or soaps, and that this also occurs in jaundice and in other pathologic conditions, with the exception of cases in which the pancreatic secretion is diminished or is prevented from reaching the intestine.

In such cases the decomposition into fatty acids and soaps is greatly diminished; the average in three cases was found by Mueller[6] to be only 39.19 per cent., instead of 75.8 per cent.*

A deficient splitting-up of the ingested fat into fatty acids and soaps, therefore, would seem to be the only fact, so far as the feces are concerned, which points with certainty to the absence of the pancreatic secretion in the intestinal digestion. In Case VII. the fatty acids and the soaps in the feces were considerably below the normal amount.

5. The presence or absence of jaundice in itself cannot be considered of diagnostic import. It is absent in a large number of cases of cholelithiasis; it may be present in pancreatic lithiasis. Jaundice in pancreatic lithiasis permits of a simple explanation. The large pancreatic duct and the common bile-duct are separated near their junction only by a thin membranous septum, and a calculus impacted in the terminal portion of the former might readily suffice to occlude the ductus choledochus by pressure. Again, a concretion small enough to pass through the pancreatic duct may be too large to pass through the duodenal orifice.

6. *Glycosuria.* It is well known that a glycosuria associated with obstruction of the pancreatic ducts by calculi or otherwise is the result of the superinduced interstitial pancreatitis, and the recent investigations of Opie[13] indicate that in the interlobular form, which is the prevalent form in such occlusions, glycosuria apparently only occurs when the sclerotic process has reached a very advanced grade.

The absence of glycosuria, therefore, can be regarded only as a

* Deuscher[11] and Albu,[12] in three observations of pancreatic disease, claim to have found no departure from the normal.

negative sign in the diagnosis of pancreatic lithiasis. Its presence is certainly suggestive.

The decisive evidence of the existence of pancreatic lithiasis in the recovery of the characteristic concretions from the stools, it has been shown, is exceedingly rare. This may be due partly to the composition of the calculi; they are small, very easily disintegrated, and may pass from the bowels in fragments or particles not readily recognized. In a number of reported cases minute gritty particles have been found in the smaller ducts, with or without the presence of larger concretions in the main ducts. If the symptoms described, with the single exception of the presence of the pancreatic concretions in the stools, separately fail to furnish evidence of pancreatic lithiasis, their various combinations may be diagnostically suggestive.

Attacks of epigastric colic of an obscure nature, with or without jaundice, associated with large numbers of muscle fibers in the stools, accompanied or followed by a glycosuria, should be regarded as a reasonable basis for a diagnosis of pancreatic lithiasis.

Mueller's investigations indicate that a greatly diminished splitting-up of the ingested fat *per se* positively indicates the absence of pancreatic juice in the intestinal digestion. In this case, therefore, in the absence of a cachexia or physical signs of a neoplasm of the pancreas or of the neighboring organs, which would occlude the ducts by pressure, a pancreatic lithiasis should be suspected.

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DISCUSSION.

DR. JANEWAY: I saw this lady at a time shortly after the passage of the pancreatic calculi and when her memory was still fresh about the position and character of the pain. It had been supposed that her attacks were of biliary colic. On an inspection of the stones which had been passed I doubted their origin in the biliary passages, and a chemical examination failed to reveal either cholesterin or biliary pigment, but showed their composition to be of phosphate and carbonate of lime. This led me to consider them of pancreatic origin. She was at that time under the care of another physician, with whom I saw her in consultation. When I saw her again with Dr. Kinnicutt, at the time of the passage of the biliary calculi, there was no notable difference in character of pains described. She was jaundiced in this attack, but not in the previous one. Dr. Kinnicutt has gone so fully into the matter that I will not burden you further.

INTESTINAL HEMORRHAGE: ITS RELATION TO DUODENAL ULCER.

By HENRY JACKSON, M.D.,
OF BOSTON.

Intestinal hemorrhage may occur suddenly in patients who have not considered themselves seriously sick, and the severity may be such that death is imminent. Its source may be obscure, cases coming under our observation in which no diagnosis can be made during life as to the exact pathologic condition which is present.

It may be dependent upon a hemorrhagic diathesis, as in most cases of the melena of early life.

Profuse hemorrhage may be the result of great engorgement of the bloodvessels of the whole gastrointestinal tract, as, first, in heart disease, and, second, in local engorgement secondary to cirrhosis of the liver. The former condition is rare and the latter common, and may be the first symptom which calls the attention of the physician to a cirrhosis of the liver which hitherto has given rise to no symptoms noticed by the patient.

Aside from the diseases mentioned in which intestinal hemorrhage occurs independently of local lesion, I have known of fatal hemorrhage in a case of advanced interstitial nephritis unrecognized until just before death, and have seen severe intestinal hemorrhage in a case of acute lymphatic leukemia that was admitted to my service as a probable case of typhoid fever. In the latter case the diagnosis was made in the course of a routine blood examination, and death followed in a few days from hemorrhage, essentially from the bowel and the bladder. Autopsy furnished no clue to the local source of the hemorrhage.

Intestinal hemorrhage may be the result of the ulceration of malignant growths in which vessels of considerable size are opened. The

hemorrhage of typhoid fever is not under consideration in this paper. Finally, we have hemorrhage from the round, peptic ulcer of the stomach and duodenum.

The difficulties of diagnosis are great, as blood may be vomited in intestinal hemorrhage from ulcer of the duodenum, while blood is frequently passed by the rectum in hemorrhage from a gastric ulcer.

The following cases are presented because of the interest attached to the differential diagnosis and to emphasize the treatment followed by temporary recovery in individuals who all showed symptoms suggestive of impending death from the immediate effects of profuse hemorrhage:

CASE I.—John R., aged forty-two years; laborer. Entered the hospital July 11, 1901. Family history negative. Previous history negative. Used alcohol moderately. July 13th he was nauseated, and vomited several times. July 14th he was no better, with continued vomiting; at night, for the first time, he vomited dark, clotted blood. July 15th he had a large black dejection, and again vomited blood. On entrance to the hospital he was pale, felt weak and faint; no dyspnea or dizziness.

Physical Examination. Respiration 20, sighing in character. Mucous membranes very pale. Pulse 130. Heart and lungs not abnormal. Liver dulness extended below the ribs to three inches above the umbilicus. There was marked tenderness at the epigastrium, and pressure caused nausea.

Four hours after entrance he vomited a pint of clotted and fluid blood; half an hour later half a pint. His condition became very poor; the pulse was 150 and intermittent. Three pints of salt solution were given under the breast, and the foot of the bed was raised.

July 17*th.* Pulse better; dark feces were washed from the rectum. Nutritive enema every six hours.

18*th.* He had some color in the face; thirst was intense.

22*d.* No thirst; no vomiting; pulse 80 and of good volume.

23*d.* For the first time a small quantity of water was allowed by the mouth.

24*th.* Milk and lime water, half an ounce every two hours.

26*th.* Stools were of natural color. Milk and lime water, one ounce every two hours.

30*th.* Four ounces by mouth.

August 8*th.* Nutritive enema reduced to two each day.

12*th.* A diet of liquids and soft solids allowed. At his request he was discharged as relieved.

The diagnosis was obscure. According to the history he had not been a hard drinker or a constant drinker of moderate daily quantities of alcohol. So far as judgment may be arrived at by personal observation, he did not present the appearance of an individual suffering from alcoholic excess. The liver was enlarged, but there was no enlargement of the spleen or superficial veins.

Cirrhosis of the liver was certainly possible, but treatment was instituted on the theory that the hemorrhage came from an ulcer of the stomach or the duodenum. The absence of any pre-existing pain in the stomach suggested to me the probability of an ulcer of the duodenum rather than an ulcer of the stomach. Further vomiting continued for two days before blood appeared in the vomitus, and the blood was dark when it appeared, and not bright red, as we usually expect in hemorrhage from an ulcer of the stomach.

I made a diagnosis of ulcer of the duodenum, though now, after I have made a careful examination of the cases shown by autopsy to be ulcer of the duodenum and reviewed the literature of the subject, I feel sure that this diagnosis can only be made with much reserve.

CASE II.—Samuel G., aged twenty-four years; a Jew. Entered the hospital June 12, 1900.

Previous History. He had never been sick; he had not used alcohol. In the night of June 11th, without warning, he vomited a large amount of dark material, and again at six and eight o'clock on the morning of June 12th. No symptoms of indigestion and no pain. On entrance he was extremely pale, respiration shallow and sighing in character. Pulse 140, barely perceptible. He appeared moribund. Morphin was given subcutaneously, and one liter of normal salt solution was given under the skin. Nothing was given by the mouth, and rectal enemata were ordered every six hours. Dr. Thorndike, who saw him in consultation, considered laparotomy as contraindicated by his serious condition.

June 13th. He had three bloody stools.

14th. He had one bloody dejection. He vomited a little, but there was no blood in the vomitus. Analysis of the vomitus showed no free hydrochloric acid, and a total acidity of 0.1186.

15th. Hemorrhage from the bowel of small amount.

20th. He was given a small amount of milk and water by the mouth.

24th. Four ounces by the mouth every four hours. No subjective symptoms.

August 5th. Sat up in a chair. August 17th he was discharged.

On entrance into the hospital his temperature was subnormal; for four days subsequently there was slight fever, and after that date a normal temperature. In three days his pulse fell from 140 to 100, and after June 17th it was 90 until convalescence was fully established.

Physical examination was absolutely negative, except for the marked anemia.

Cirrhosis of the liver was not suggested by the physical examination; he gave no history of the use of alcohol, and, further, I can say that in an extensive practice among Jews I have not seen or known of a case that suffered from the abuse of alcohol.

As in Case I., the diagnosis was obscure, being either gastric or duodenal ulcer. The absence of all symptoms suggestive of gastric ulcer, and the fact that the first blood vomited was dark, and that all the blood which subsequently passed came from the rectum, made me suggest ulcer of the duodenum as the probable source of the hemorrhage.

CASE III.—P. McC., aged forty-one years; laborer. Entered the hospital May 9, 1901.

Previous History. Daily use of alcohol, with frequent excesses.

Present Illness. For one week he had felt weak, and had a gnawing pain just to the left of the epigastrium. Three days before entrance the pain was so severe that he felt faint; the pain was accompanied by nausea, and on two occasions he vomited a little dark material.

Physical Examination. The mucous membranes were pale. Red cells, 2,252,000; whites, 15,500; hemoglobin, 30 per cent. Heart not abnormal. The liver descended below the ribs on a full breath. Just after his entrance into the hospital he vomited a little coffee grounds material, and passed ten ounces of blood by the rectum.

June 10th. He passed one pint of blood by the rectum. Nothing was given by the mouth, and rectal enemata were given every six hours. Aside from great thirst, he had no untoward symptoms after May 11th, his second day in the hospital. On May 22d a little milk and lime water were given by the mouth; this was the thirteenth day of his stay in the hospital.

12th. The patient was on full diet, and was discharged on June 17th.

The diagnosis made was hepatic cirrhosis or gastric ulcer. The history of alcoholic excess and the enlargement of the liver made cirrhosis probable. The epigastrium pain certainly suggested the possibility of gastric ulcer. He was treated as if the disease were gastric ulcer, and the rectal enemata were given for a much longer period than if he had been practically sure that the hemorrhage was the result of a cirrhosis of the liver.

Turning now to the inferences to be drawn from cases that are shown by autopsy to be ulcer of the duodenum, the clinical symptoms presented by ulcer of the stomach and ulcer of the duodenum are so similar that a positive differential diagnosis seems to me wellnigh impossible. In both of these conditions long periods of "indigestion" may precede any active symptoms, or the trouble may be present without giving rise to any symptoms. Sharp and definite pain dependent upon the ingestion of food, or brought out by palpation, is evidently not a common symptom in ulcer in my cases, or in those presented by Dr. Kinnicutt in his exhaustive article in the *Festschrift* in honor of Dr. Jacobi.

I can give no data as to the chemical analysis of the stomach contents, as no examination was made in the cases found at autopsy. In Case II., reported clinically, no free hydrochloric acid was found in the vomitus, and the total acidity was low; but inferences based on examination of the vomitus are notoriously unreliable.

Hemorrhage in my cases was not a factor of importance. Previous

to their final sickness no blood was vomited or passed by the rectum in any of the cases. Out of seven cases a little blood was vomited by four; one passed a little just before death; one had large bloody dejections, with moderate hematemesis, and in two cases no blood was vomited or passed by the rectum.

In the seven cases reported by Dr. Kinnicutt again hemorrhage was not a prominent factor in the symptomatology before they entered the hospital. One of his cases was in the hospital for five months, and had melena and hematemesis, with about equal frequency, during the whole of that time.

Pathologically the two forms of ulcer are identical, as indicated by the name usually applied by modern writers of "peptic round ulcer of the duodenum."

From a therapeutic stand-point the treatment of the two forms is identical. Absolute rest of the stomach, prohibiting all food by the mouth, and limiting water to the smallest possible amount. Morphin is at first advisable, and later may be necessary. Under this treatment vomiting may almost invariably be stopped. In addition to the nutritive enemata given, it is desirable to give daily large injections of normal salt solution by enema, to arrest thirst and assist in nourishing the patient.

If the anemia is so great that death is threatened, normal salt solutions should be given subcutaneously, in half-liter amounts, until the pulse indicates that the crisis has passed. Theoretically the subcutaneous injection of salt water into the tissues may increase the liability of increasing hemorrhage or starting up a bleeding which has already stopped; practically this has not been my experience either in the class of cases cited in this paper or when I have used the method in severe hemorrhage from typhoidal ulcers. It is my impression that we have in salt infusion a powerful means of saving life after dangerous hemorrhage, a method devoid absolutely of danger and potent for good.

When large amounts of saline solution are given by the rectum, especially if reinforced by the subcutaneous injections of salt solution, patients do not suffer intolerably from thirst, even when no food is given by the mouth.

The prevention of nausea and vomiting by rectal feeding is evidently quite as important as the removal of possible irritation of the

stomach by food. It seems unlikely that milk and lime water could act as a local irritant to an ulcer of the stomach that is necessarily constantly exposed to the more irritant gastric juice.

Seven Cases in which Duodenal Ulcer was Found on Postmortem Examination.

CASE I.—J. S., aged thirty-six years; a laborer. Entered the surgical wards August 19, 1899.

Family history not important.

Previous History. For fifteen years he had suffered from some stomach trouble, so that he had been obliged to be careful as to his diet.

On August 12th the patient had vomited, and a small amount of bright blood was seen in the vomitus. On August 11th, the night before he entered the hospital, he had a violent pain in the epigastrium, which was followed by profuse vomiting, with a little blood.

Physical Examination. Temperature, 104°; pulse, 80. He seemed very sick. The abdomen was rigid, and there was marked tenderness at the epigastrium. Exploratory laparotomy was urged, but refused.

August 20th. The incision was made at the epigastrium. The omentum was bound down by adhesions walling off a cavity in which were pus and particles of food. A perforation was found in the duodenum near the pylorus. Before the operation perforation of an ulcer of the stomach was considered the most probable cause of the acute peritonitis which was evidently present. Death occurred within twelve hours.

Autopsy. A small opening 5 cm. in diameter, with clean-cut edges, was found just below the pylorus. There was also another small, shallow ulcer in the duodenum on the anterior surface. Acute general peritonitis; parenchymatous degeneration of the kidney; acute splenic tumor; emphysema; hypertrophy of the right ventricle.

CASE II.—C. R., aged fifty-nine years; a piano polisher. Entered the surgical wards December 5, 1899.

Family history not important.

Previous History. For several months he had had distress in the stomach, especially before meals. There was no vomiting. The distress was usually relieved by food. Ten days before he entered the hospital he had an unusually severe attack of indigestion.

December 4th. On the night before he entered the hospital he had sudden pain at the epigastrium, but did not vomit.

5th. The patient vomited several times, but there was no blood in the vomitus.

Physical Examination. The pulse was rapid and poor. The abdomen was distended and rigid, with general tenderness. The knees were flexed. There was decidedly localized tenderness just to the right of the median line in the epigastrium. At the operation a perforation was found in the duodenum. He rallied from the operation, but died on December 8th. Again no diag-

nosis was possible, though perforated ulcer of the stomach was considered as possible.

Autopsy. In the duodenum a small perforated ulcer was found just below the pylorus. There was a second small ulcer in the duodenum on the level of the upper margin of the perforated ulcer. The other organs were not abnormal. Acute general peritonitis.

CASE III.—T. W. H., aged forty years; a blacksmith. Entered the surgical wards May 20, 1901.

Family history was not important.

Previous History. For several years he had dyspepsia. He had never vomited. Since May 1st he had felt sick, with loss of appetite, occasional vomiting and distress at the epigastrium, but had no pain. Twenty-four hours before he entered the hospital he had a sudden sharp pain in the epigastrium, which increased steadily and extended throughout the abdomen. There was much nausea, but he could not vomit. There was no dejection for four days.

Physical Examination. The abdomen was distended, rigid, tympanitic, and tender all over. In view of the fact that a very large number of obscure cases of general peritonitis have their origin in the appendix, an incision was made over the appendix. This was found to be normal. The peritoneal cavity was found inflamed, and contained a small amount of pus which was evenly distributed over the intestines. Another incision was made at the epigastrium, and a small perforation was found in the greater curvature of the stomach. The perforation was closed and the abdominal cavity was flushed with sterile water. For two days the vomiting continued, and the pulse was poor in quality. On the second day the skin was cold and clammy, and death ensued.

In this case no diagnosis was made, and ulcer of the duodenum could not have been thought of as likely. The record shows that appendicitis was looked upon as a probable cause of the acute peritonitis which was evidently present.

Autopsy. In the stomach near the pylorus a small perforation was closed by suture. In the duodenum were two deep, punched-out ulcers. One reached to the periduodenal connective tissues, and in fact to the pancreas. In the center of the other was a perforation. There was acute localized peritonitis, with a pocket of pus between the liver and the diaphragm. Acute bronchopneumonia; chronic fibrous pleurisy; chronic pulmonary tuberculosis; chronic diffuse nephritis.

CASE IV.—W. O., aged fifty-seven years; a painter. Entered the medical wards December 15, 1900. Family and previous history negative. On December 14th he had cramp in the epigastric region, which grew rapidly worse; the pain was colicky in character, and was accompanied by shortness of breath.

Physical Examination. Pulmonary examination negative on the left side. On the right side respiratory murmur much diminished, and was accom-

panied by coarse friction sounds over the lower front and axillary regions. The heart was not abnormal. The abdomen was soft and full. There was much pain along the right costal margin. There was no pain or tenderness at McBurney's point. Leucocytes, 22,400.

December 17th, two days after his entrance into the hospital, he vomited occasionally, the vomitus consisting of a dark, soot-colored fluid. There was sharp colicky pain in the abdomen. He was apparently doing well, when he suddenly vomited, and died in two minutes.

In this case the diagnosis was absolutely obscure. There were no symptoms suggestive even of ulcer, and the acute peritonitis was not marked by prominent or distinctive symptoms. The only diagnosis that could be definitely made was acute pleurisy.

Autopsy. On the anterior surface of the first portion of the duodenum, 3 cm. from the pylorus, was an opening 2 mm. in diameter. There was no thickening of the duodenal wall about the perforation. Acute general fibrinous peritonitis; acute pleurisy on the right side.

In the four cases just cited death was the direct result of acute general peritonitis secondary to perforation of the duodenal ulcer, yet in none of the cases were the symptoms previous to the perforation such as to lead one to diagnose the existence of an ulcer in this region.

In two of the three following cases the ulceration certainly was of no etiologic importance in the fatal issue, and it is probable that in the third case the ulceration may be looked upon as a complication of minor importance.

CASE V.—J. H., a woman, aged thirty-five years. The family history was good. She was eight months pregnant, and during her pregnancy had had but little nausea and no vomiting.

September 1st. The patient had a chill, followed by excessive vomiting, later followed by a scarlet rash.

2*d.* Admitted to the scarlet fever wards of the City Hospital, South Department. She was well developed and nourished; moderate prostration; no septic odor.

4*th.* Had a poor night, and complained of a severe pain in the left side, which was not relieved by moderate doses of opium. She vomited a greenish fluid.

6*th.* Labor pains, followed by delivery.

7*th.* Coffee grounds vomitus. Had most pain in the left side. Later in the day she vomited clotted blood and had tarry stools.

8*th.* Toward night she complained of much thirst, and said: "What is the matter with me? I am dying! Give me a bed-pan; everything is coming away." She died in a few moments.

Autopsy. In the duodenum, 3 cm. below the pylorus, were three losses of substance about 1 cm. in diameter, with clear and apparently healing bases. Pyonephrosis of the left kidney, with a purulent process behind the pancreas; pyelitis with calculi. Pyelonephritis of the right kidney. Acute splenic tumor. Intestines normal, except for the ulcers.

Previous to the hemorrhage the presence of ulceration could not have been suspected. The pain was evidently due to the renal condition. The clinical history certainly suggests death from a large hemorrhage, yet the autopsy distinctly states that the intestines were normal, except for the ulcers mentioned.

CASE VI.—A woman, aged seventy years, entered the medical wards April 22, 1897. She was admitted for heart disease, and for four days had symptoms of extreme heart failure. There were no symptoms in her previous history or in her final illness suggestive of any stomach or bowel trouble.

Autopsy. In the stomach near the pylorus were two small ulcers. In the duodenum, 5 cm. below the pylorus, were three somewhat similar ulcers, with injections of the surrounding walls. The ulcers of the duodenum extended down into the submucous coat among the glands; there was necrosis of tissue beneath the ulcerations, with hemorrhage and large masses of fibrin. No micro-organisms. There was fluid in the various serous cavities. Heart, 510 grams. Aortic and mitral disease. Chronic passive congestion of the liver, kidneys, and spleen.

CASE VII.—A. P., aged fifty-seven years; a clergyman. Previous history of acute articular rheumatism in youth, and again in 1899. He entered the hospital July 28, 1900, on account of dyspnea, cough, and edema. His heart was much dilated, 7 cm. to the right and 14.5 cm. to the left of the mid-sternal line. He was discharged, relieved, in three weeks. He re-entered January 24, 1901, six months later, with marked dyspnea and cyanosis. During the two days that he was in the hospital he had black dejections in which hemin crystals were found. He died suddenly on the sixth day.

Autopsy. In the stomach and intestines there was dark-red blood. In the stomach was one punched-out ulceration, 3 cm. by 4 cm., also two smaller ulcers. In the duodenum just beyond the pylorus were two ulcers similar to those in the stomach. Heart, 605 grams. Aortic and mitral disease Chronic passive congestion of the liver, kidneys, and spleen. 1000 c.c. of fluid in the right pleural cavity; the left was obliterated.

The final issue of this case was probably directly due to hemorrhage from one or more of the ulcers, but previous to his last illness there were no symptoms suggestive of ulceration in the gastroduodenal tract.

RÉSUMÉ OF SEVEN CASES IN WHICH ULCER OF THE DUODENUM WAS FOUND AT AUTOPSY.

Age and sex.	Previous history.	Last illness.	Ulcer found.	Other organs.
Case I. Man, 36	For fifteen years had indigestion.	For weeks had vomiting; little blood; acute epigastric pain.	Two in the duodenum, one perforated.	Acute general peritonitis; splenic tumor; hypertrophy in right ventricle.
Case II Man, 59	Several months had distress in stomach; no vomiting.	For twenty-four hours had sharp epigastric pain; no blood, but vomiting.	Two in the duodenum, one perforated.	Acute general peritonitis; other organs not abnormal.
Case III. Man, 40	Several years had "dyspepsia;" no vomiting.	Three weeks had occasional vomiting; one day had sharp epigastric pain; small amount of blood vomited.	One perforated in the stomach; had two in the duodenum; one perforated.	Acute localized peritonitis; chronic pleurisy; chronic pulmonary tuberculosis; chronic diffuse nephritis.
Case IV. Man, 57	No symptoms suggestive of digestive trouble.	One day had sharp epigastric pain, with dyspnea; little blood vomited.	One perforated in the duodenum.	Acute general peritonitis; acute pleurisy on the right side.
Case V. Woman, 85	No symptoms suggestive of stomach trouble.	Scarlet fever; little blood vomited and passed by rectum.	Three in the duodenum.	Pyonephrosis of left kidney; acute splenic tumor.
Case VI. Woman, 70	History of heart failure: no stomach symptoms.	No symptoms suggestive of stomach trouble.	Two in the stomach; three in the duodenum.	Aortic and mitral disease; chronic passive congestion of various organs.
Case VII. Man, 67	History of heart failure.	In last two days of life passed a little blood by the rectum.	Three in the stomach; two in the duodenum.	Much blood in the stomach and intestines; aortic and mitral disease; chronic passive congestion of various organs.

In these seven cases five were men and two were women. Three presented symptoms suggestive of some digestive trouble of a vague character usually described as indigestion. In four no symptoms existed suggestive of any gastrointestinal disturbance. In four cases death resulted from a perforation which occurred from one to three days before admission to the hospital, and was signalized by a sudden sharp pain in the epigastrium, accompanied by nausea, and in two cases by vomiting.

In six cases the ulcers in the duodenum were multiple, and in three there were ulcers in the stomach as well.

In two cases only were there lesions in other organs which might have had an etiologic bearing in the causation of the ulcers—namely, two cases with hypertrophy and dilatation of the heart accompanied by symptoms of gradual failure for months or years.

In none of the cases was a diagnosis of ulcer of the duodenum made, and in none was such a diagnosis possible even in the light of the postmortem examination.

In three cases the lesion was considered to be perforation of an ulcer of the stomach; in one case appendicitis was considered probable; in one case no diagnosis was made.

In two cases—those with heart failure—no symptoms suggested ulcer of the duodenum.

In view of the histories of my cases, and also those of Dr. Kinnicutt, it is reasonable to consider that large hemorrhages, either from the stomach or bowel, are more likely to be dependent upon ulcer of the stomach or some other pathologic lesion than ulcer of the duodenum. Perforation is more common in ulcer of the duodenum than in ulcer of the stomach.

DISCUSSION.

DR. KINNICUTT: I would just add a word in regard to my clinical experience in the use of saline solutions. We have used them in just such cases, and with other forms of hemorrhage, and always with decidedly good effect.

DR. THOMSON: The thought occurs to me that the diagnosis of ulcers of the duodenum is more or less problematic, and yet I think we have some indications that point to such a lesion, and more than once I have had those indications lead to a diagnosis which was confirmed at the postmortem examination. The first is, that ulcer of the duodenum is so much more common in man, a contrast in that particular with ulcers of the stomach. Secondly, on the cases I have made the diagnosis there were not the same symptoms on palpation referred to the stomach, and in none of the cases was hemorrhage a distinguishing symptom.

DRAINAGE IN CHRONIC INTESTINAL CATARRH: ITS IMPORTANCE AND TECHNIC.

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CHRONIC intestinal catarrh as we meet with it in practice and as we understand it all too poorly is usually restricted to the colon. That catarrh of the small intestine occurs there can be little doubt, for catarrh probably is a disorder which attacks at some time or other every mucous membrane of the body; but the symptoms and signs that we can identify as belonging to chronic catarrh of the bowels nearly all point to the region below the ileocecal valve.

This disease is very common (the most common of the chronic affections), produces quite a variety of symptoms, and is responsible for many collateral and widely variant disorders of other organs and systems of organs. These include debility, discomfort, pain in the abdomen, colicky symptoms, alternations of constipation and diarrhea, bloody passages, hemorrhoids, tenesmus, insomnia, mental apathy and incapacity, and actual melancholia. It occasionally destroys life indirectly by lowering vitality and making the body a victim to some intercurrent disease. It occurs to nearly all ages of life and to both sexes. Infants have it (as shown by repeated mucous discharges) as well as adults.

Numerous influences conspire to produce it, prominent among them being indigestion in the stomach and small intestine, irritating things in the colon (chiefly irritating, ill-conditioned feces), general debility, and perhaps poisons accidentally acquired. It is also often produced, as it is usually perpetuated, by failure of frequent, regular, and complete evacuation of fecal matter from the colon itself. Lack of efficient drainage from the colon is a prolific source of mischief in this as well as other directions. Decomposing

retained fecal matter, or matter unchanged and that merely acts as a foreign body, is capable of keeping up a catarrh almost indefinitely.

Some degree of constipation, involving a part or all of the colon, is a much more common condition than is usually supposed, and it is responsible for many more catarrhal symptoms than we have been ready to believe. Many people in fair health, who suppose themselves to have daily and sufficient alvine evacuations, are almost constantly carrying in the colon above the sigmoid flexure a large amount of feces that do various kinds and degrees of mischief, including the production of chronic catarrh and ptosis of the transverse colon. This condition is demonstrable in many people by the use of a large enema immediately after a supposedly complete evacuation, showing that the colon was loaded.

Nor is it surprising that such should be the case when we consider the numerous sacculations of the colon, its great distensibility, and the several flexures at differing angles along its course, as well as the nervous and muscular sluggishness that the colon itself frequently shows. It is surprising rather, when we consider the anatomy and physiology of the colon and the artificial lives we all live, as well as the unwholesome ones some of us have, that the catarrhs and constipation are not more rather than less frequent.

If these postulates are correct, then regular evacuations, harmless and complete, are more useful than any other measure for the cure of chronic catarrh of the colon and for its prevention and the prevention of its recurrence. This measure assists more than any other the normal physiologic forces of the parts involved, which forces always, when unimpeded, tend to prevent catarrh and to cure it when it exists. Many of us in treating this disease seem to have forgotten that there is such a thing as innate physiologic power in the colon that works toward keeping the functions normal, and is capable of doing this if it has a fair chance. As a result, we have prescribed various astringent drugs—so-called but not real intestinal antiseptics, and other hoped to be or wished to be panaceas or specifics—and wondered why the disease did not disappear, and when gone stay gone.

It ought to be a cardinal doctrine in the treatment of this affection that no other treatment is in order until the aforesaid regular,

free, and harmless evacuations are provided for; otherwise free drainage, and not even then if these measures are sufficient. That they often are sufficient is a fact abundantly proved. The modern scientific treatment of disease aims in general to brush away the causes and remove the obstacles to recovery as far as possible, and to see if the latter does not take place. There is not the slightest reason why this rule should not be followed with catarrh of the intestines. It is always safe, conservative, and wise, and does not bar or prejudice any other and useful treatment that may be found necessary afterward.

When constipation is manifest, whether there are the symptoms of catarrh or not, the measures for relief are usually restricted to so-called laxative drugs, to suppositories and enemas, and occasionally to massage and mental efforts to induce regularity of habits. These measures are all more or less efficacious when used with caution, regularity, and faithfulness. Many of the foods used are laxative because indigestible; most of the laxative drugs are used without system, according to the inclination of the patient from day to day, and usually prompted by the symptoms of biliousness, and are commonly taken in cathartic doses rather than such as might act as a tonic to the intestinal mucous membrane. The suppositories, enemas, and other measures are subject to similar drawbacks. But, in spite of all this, the measures have done a vast deal more of good than harm, only much less good than some of them are capable of doing if used in the right way.

No routine treatment of catarrh of the colon is worthy of the widest confidence, although perfect and daily drainage as a principle of treatment is of the greatest consequence. Each case should be pondered by itself and a treatment adopted in accordance with its needs, but the principle of drainage ought to be insisted on in every case. It needs to be insisted on so strenuously that it is worth while to catalogue the indications that point to the need of better drainage, some of the obstacles to its accomplishment, and the basal facts in the technic that belong to it.

In general there is need for better drainage when it is known that there is liable to be accumulated fecal matter anywhere in the large intestine. Various signs point to this condition. To bring away considerable masses of fecal matter from the colon by an

enema or by a quick saline cathartic after the patient has supposed his colon to have been emptied is proof positive; and one experience of this sort proves the possibility of the frequent existence of the trouble, especially in the presence of other symptoms.

To find scybala among—especially after—the passages of softened material is evidence of the retention of fecal matter in some intestinal pocket longer than is good for a catarrh; and scybala mixed with mucus is a positive demonstration of this fact. The colon is a reservoir for the storage of fecal matter for an indeterminate time when in health; but when in the condition of chronic catarrh no such material should remain long enough to become hardened, and the hardening process begins very promptly in and near the region of catarrh. If the retention occurs just above the seat of the disease it is nearly as bad as though within it, for so situated the hard masses probably interfere with the return circulation from points below.

Colicky pains, whether slight or severe, are usually in the colon, they nearly always signify difficulty in moving fecal matter forward, and as unmistakably indicate the necessity of some measure of assistance.

Intestinal flatulence, especially the discharge of fetid gas, always means the same thing. In case of either colicky pains or fetid flatulence an enema is nearly always followed by a prompt discharge of fecal matter, with as prompt relief of all the symptoms.

General discomfort in the abdomen or in the back, tenderness at some localized point in the abdomen, and rectal tenesmus, all suggest lack of drainage from some point in or above the sigmoid, and these symptoms should never be permitted to last long without testing the point with an enema or a laxative. Insomnia, mental heaviness or irritability, nervous disomfort in the lower extremities, and inability to keep the legs still often point to the need of a free evacuation of the colon, the symptoms disappearing the moment this end is accomplished.

Diarrhea may continue for days, to disappear as soon as the whole of the colon is evacuated daily and without irritation.

Obstacles to the practical accomplishment of free drainage are numerous. First is to know the right thing to do; to understand the sequence in which the different measures that are sometimes

useful should be tried; then to appreciate some of the anatomic and physiologic difficulties is not always easy, and the lack of constancy on the part of the average patient in carrying out the best measures is the worst obstacle of all.

Sagging of the colon (enteroptosis) is one of the anatomic obstacles. It exaggerates the splenic and hepatic flexures and makes it difficult for the contents to pass them. More than the usually expended peristaltic force is required to empty the colon, and the power of the intestine in this direction is usually reduced.

Then there is at times great muscular apathy in the intestinal wall. When this or the ptosis exists we have a positive obstacle. The obstacle is most apparent at the flexures, of which there are several—the hepatic, the splenic, one at the lower end of the descending colon, where the gut curves forward into the false pelvis, and several flexures of and about the sigmoid proper. These last differ in different people—as the sigmoid differs in length, position, and curves.

The tetanic rigidity of the colon which is often found in regions of this tube in chronic catarrh, and whose pathology is so far a mystery, often impedes the movement of the contents downward, as it causes pain in the process. This state of rigidity often continues for hours and even days. Probably its most common location is the descending colon and sigmoid. It fluctuates from moment to moment, and does not always relax completely to let fecal matter pass, but often forces it through its narrowed lumen in small particles, with acute pain. This fact can easily be demonstrated by palpation by anyone, even by the patient himself, in a positive case with rather thin abdominal walls.

The vertical posture of the body for two-thirds of the time of our lives hinders the easy evacuation of the colon. Since we have ceased to walk on all-fours we are at a disadvantage as compared with the lower animals. Our habitual posture increases the enteroptosis, and so tends to increase any stretching of the transverse colon and any irritations at the splenic flexure, and provokes countless cases of catarrh. It also frequently increases the obstacles of the lower flexures and the rectum.

The means to accomplish drainage should be employed regularly, not fitfully, nor merely when the patient feels like it. If

laxative medicines are used—and there is no objection to them, even as a beginning treatment—they should be taken not in cathartic, but laxative doses, and daily or twice a day, as may seem best; never to produce griping, aching, or tenesmus. No unyielding rule can be made for the selection of the right drug, since patients have so many personal idiosyncrasies. The salines agree best with some, the vegetable laxatives with others. Of the latter, cascara, rhubarb, senna, and aloes are the best. They are usually taken in too large doses. Two weeks' trial with any one of them is probably a sufficient test. The oils sometimes act best of all. Olive oil (in large, regular doses) is the most rational for a constant laxative, although castor oil agrees with some patients perfectly; while a large daily dose of pure vaselin (2 or 3 drachms) is sometimes a most successful medicine. Of the salines, probably the best are magnesium sulphate, sodium sulphate, and sodium phosphate.

Coarse food and indigestible substances seem to be beneficial for some constipated patients; they induce daily dejections without harm, but they are a poor resort for the patient with intestinal catarrh. Moreover, with the debilitated patient, and especially in rectal constipation, they are liable to induce abscesses.

The psychic method of securing (or trying to) a daily evacuation by going to stool regularly and trying is rarely successful in chronic catarrh of the colon. It is a good measure for people in health who have sluggish bowels; it may prevent catarrh, hemorrhoids, and ischiorectal abscesses, and is much to be commended for this purpose, and in proportion to the few people who practice it regularly it is often successful.

For the catarrhal cases usually some artificial aid is necessary; even in those with diarrhea there are often hardish fecal masses retained in some pockets or sacculations, and the retention of which aggravates the diarrhea. In many such cases there is a marked irritability of the rectum and sigmoid, compelling the prompt evacuation of every particle of substance the moment it enters them, while just above are often retained hard masses that help to continue the diarrhea. In all such cases there should be secured occasionally a free evacuation of the entire colon, either by castor oil or a normal salt solution enema. Sometimes the great irrita-

bility of the rectum makes it extremely difficult to use the enema successfully; and sometimes the tetanic rigidity of the upper sigmoid and descending colon offers a serious obstacle to the inflow of water, pain and tenesmus occurring unless the current is very slow.

For the purpose of drainage in chronic catarrh no other measure is so generally useful as enemas properly and regularly taken and managed rationally, and especially when aided by the use of posture to secure evacuation. The enema should be used daily or twice a day, as seems necessary. No harm will ever come to the intestine if the water is warm enough, is introduced slowly to avoid colicky peristalsis, and never pushed to the point of causing pain by distention; especially is this true if the normal salt solution is used.

The enema should be taken with the body horizontal, and preferably on the left side at beginning. As soon as the fluid reaches the splenic flexure it is liable to cause more discomfort and tenesmus as it rises into the transverse colon. This is a sign to the patient to turn upon his back, which usually relieves these feelings and allows the enema to flow painlessly clear to the end of the cecum. Next to the completely horizontal posture, the preferable one for taking the enema is that with the body bent far forward while seated on the closet.

The best enema for daily use is plain water or normal salt solution (a heaping teaspoonful of salt to a quart).[1] This latter never irritates the intestine; indeed, it is so soothing to the mucous membrane that sometimes the intestine forgets to expel it, and the enema is long retained and discharged in repeated small portions, to the inconvenience of the patient. In such cases either pure water or a stronger salt solution may be used.

The normal salt solution has an excellent effect on the catarrhal surfaces; it washes away mucus and comforts the irritated spots. The best temperature of the enema for the average patient is 100° to 105° F. A few vigorous patients find good effect from cold or cool injections, and doubtless these do often provoke quick action;

[1] The later investigations seem to show that the true normal salt solution contains nearly if not quite 9 parts of common salt, instead of six, to the 1000 of water. This requires 135 grains to a quart, which is about a heaping teaspoonful.

but most catarrh patients are reduced in vitality, and the warm enemas are better for them. A fountain syringe should always be used, and, if possible, a quart of water at least be introduced into the bowel—for an adult patient—and no effort should be made to retain it for any length of time. There is a lay theory abroad that an enema must, in order to be effective, be retained several hours before being expelled, and any patient is liable to have heard of it and be misled by it unless warned by the physician. Patients sometimes suffer for hours in the foolish attempt to retain large quantities of water in the colon, and then complain that they cannot take enemas without pain. The theory is, of course, as senseless as that other one that an enema habit may be formed which will be calamitous.

Sometimes in taking an enema a little fecal matter in the rectum will cause an extreme degree of tenesmus after a few ounces of water have been introduced; then it is best to stop and expel this, when the intestine may accept a quart or more (introduced slowly) without special discomfort, and a free movement from the upper regions of the colon be induced. Attempts to take the enema in the sitting posture or with a rapid flow may cause similar tenesmus and it may be quite impossible to fill the colon to the splenic flexure.

The usual posture of the body and the normal and abnormal anatomic conditions often make the colon difficult to empty thoroughly, even with the aid of an enema. The enema is sometimes retained, causing occasional colicky pains, and similar discomfort is produced or increased by attempts to expel the accumulation.

Posture of the body as a factor in the action of the intestine, and especially in the evacuation of it, is not enough studied or enough taken advantage of.

One of the most remarkable effects of posture is shown, I think, when the body is, at stool, thrown forward so that the anterior wall of the abdomen is nearly horizontal. This maneuver conduces to a freer and prompter evacuation in health ; it lessens the colicky pains with which a catarrhal colon is evacuated, and facilitates the process ; it tends to prevent an annoyance that often occurs in these cases, consisting in retention of a portion of an enema, which may be expelled in small instalments at successive sittings afterward, and often with more or less discomfort of a colicky character.

The explanation of some of the effects referred to is easy to see. The forward position allows the sagging transverse colon to come back to or toward its normal position, and its flexures (the hepatic and splenic) to be somewhat relieved of strain, so that the contents may pass more easily. By this posture the lower forward curve of the descending colon, the upward curve (when there is one) of the sigmoid, and the rectum, with the short side of its curve forward—all have the force of gravity in their favor in efforts to evacuate, and can the more easily unkink their flexures, and so lessen colicky pains and obstruction. Colicky pains are prone to occur most at the flexures and sharpest turns of the intestine, and at the points of tetanic rigidity, where, of course, most peristaltic force is required. Experiences of this kind tend to prove that the erect or sitting posture is a physical disadvantage in efforts to evacuate the colon and rectum, and that the contention is correct that the animals that walk on all-fours, the bodies of which are always horizontal, have distinct physical advantages over us in the ease with which their functions are performed.

The dorsal decubitus ought to relieve the difficulties of the transverse colon and its flexures, and doubtless does, but it is a gravity obstacle to the lower descending colon and the rectum, and is of incomparably less value than the forward position as an aid to drainage.

Sometimes a patient is annoyed for hours by flatulence that shows itself by the discharge of a bubble of gas, usually fetid, every few minutes, and with no inclination for a movement of the bowels. Then by sitting at stool with the body bent forward an evacuation is secured within a few minutes. This occurs even after he has been straining at stool in the erect posture with only discomfort, and no evacuation or inclination to one.

The repeated discharge of fetid gas, or any considerable quantity of odorless gas, should lead to prompt efforts for an evacuation; that is to say, the presence of gas shows that usually the large intestine is more or less loaded with fecal matter that should be gotten rid of, and which the intestine is not harboring or storing in the physiologic way. The normal way is without development of malodorous gas in any quantity.

Occasionally a patient has slight colicky pains in efforts to evac-

uate fecal matter or an enema that has just been taken, and these pains may be attended by a sense of nausea or faintness. The colic, the nausea, and faintness are reduced or abolished by the extreme forward position of the body. One patient has repeatedly demonstrated this proposition by bending his body forward when it has happened that the colic or the other sensations have occurred at stool, and with the result that the disagreeable feelings have promptly ceased and the evacuation as promptly ensued. He has learned that this maneuver will relieve him of distress, and help the bowel to evacuate itself.

In most cases of catarrh where there is any degree of enteroptosis some benefit may be derived from a firm bandage worn about the lower abdomen. It lessens and represses the deformity to a slight degree, and so far facilitates drainage as well as better circulation in the intestine, and hence improves the tendency to recover. And probably there is some dragging down of the transverse colon as well as of the stomach in most of these cases.

The wearing of an abdominal bandage has been rather fashionable in certain quarters, usually on the theory that it prevents cold taking, diarrhea, and other diseases of the abdomen. As probably in the majority of cases the bandage is worn rather snug, it is likely that it has done more good by lessening the splanchnoptosis than in any other way. The tendency on the part of the wearer of a bandage to draw it rather firmly during the time of his daily vertical activities doubtless grows out of a sense of comfort from the support, and this latter is probably due to a relief from the pull downward of the organs.

The best form of bandage is one made of elastic material and to fit firmly about the lower part of the abdomen. Perineal straps are usually required by thin people to keep the apparatus from sliding up out of place. Any good effect from the bandage depends on its being kept in the right position and making steady and firm pressure. If it exerts its chief force on the upper part of the abdomen it is worse than useless, for then it aggravates the splanchnoptosis, with all its misfortunes.

PNEUMOCOCCIC ARTHRITIS.

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It is a well-known fact that the diplococcus of Fraenkel is not limited, as to its habitat, to the lungs, nor, as to its effects, to the production of acute croupous pneumonia. In many of the inflammations that complicate pneumonia bacteriologic examination has revealed the same pneumococcus that induced the primary pulmonary lesion, the mode of transport from the lung to the more distant organ being made clear by the detection of the micro-organisms in the blood during life or after death. It has also been shown that pneumococcic infection with primary localization other than pulmonary may occur, *e. g.*, in the middle ear, the meninges, the valves of the heart, the joints, etc. These facts are so generally recognized as true that they need no further comment, established as they are by numerous clinical, postmortem, and experimental observations. Weichselbaum's[1] statement, made in 1888, has been repeatedly confirmed: "The diplococcus pneumoniæ can cause not alone pneumonia, but also various other processes, either at the same time as pneumonia or entirely independent of it."

There is scarcely an organ or tissue of the body that has not been mentioned as occasionally attacked by the pneumococcus either primarily or secondarily. These secondary localizations are commonly seen during or following a croupous pneumonia. Thus are recorded cases of pneumococcic tonsillitis, stomatitis, lymphadenitis, ulcerative gastritis, enteritis, peritonitis, encephalitis, meningitis, myelitis, otitis media, parotitis, cellulitis in various parts of the body, myositis, phlebitis, endocarditis, pericarditis, bronchitis, pleuritis, orchitis, ovaritis, metritis, nephritis, angiocholitis, conjunctivitis, keratitis, panophthalmitis, tenovaginitis, osteomyelitis, and arthritis. It is to the last-named pneumococcic inflammation—that of the joints—that attention is here directed.

The study of the subject is rendered easier by the fact that recently it has been very thoroughly gone into by Leroux,[2] whose monograph,

with its collection of twenty-eight cases and its collocation of facts, must of necessity be freely drawn upon in the preparation of this article. In truth, Leroux's article makes such a paper as the present one seem much like repetition and almost unnecessary; but pneumococcic arthritis has received little notice in this country, and this paper may serve to call the attention of American physicians more forcibly to this subject, and it will add a few hitherto unrecorded cases to the list of Leroux and to that of Cave,[3] who has recently reviewed the topic in England.

HISTORICAL. Stray references to arthritis occurring during the course of pneumonia are found in periodical and text-book literature before the time of the recognition of the pneumococcus. Undoubtedly many cases passed as rheumatic or as pyemic; but some observers clearly differentiated between the joint of ordinary rheumatism and this form of arthritis, with its frequent monarticular localization, its permanent rather than shifting character, the presence of fluid, and the absence of other ear-marks of rheumatism. No better illustration of such cases can be given than the ones cited by Leroux from Grisolle's *Traité de la Pneumonie*, 1864. I quote Cave's abstract: "Four patients, who had never suffered from any form of articular or muscular rheumatism, were attacked either early in the course of a pneumonia, or shortly after its subsidence, with acute arthritis, affecting in one case the two shoulders, in another the right knee, in the third the left ankle, and in the fourth the right wrist and the left knee. The last case was examined after death, and both the affected joints were distended by odorless pus, and the synovial fringes were injected. The joint affection was always a continuous one, with none of the fugitive character of true rheumatism; and after discussing the relations with this latter disease Grisolle came to the conclusion that the nature of the two affections was quite distinct."

Between 1883 and 1888 the pneumococcus was proven to be the cause of croupous pneumonia, and it was discovered also that inflammation of structures other than the lung could be produced by this organism. In 1888 Weichselbaum reviewed the whole subject of the rarer localizations of the pneumonic virus, and described the case that, with Leroux, we must look upon as the first one clearly worked out in its details, and indisputably a pneumococcic arthritis. Since that time several cases have been recorded, so that, while a relatively rare complication, there were found by Vogelius, in 1896, 11 cases; by Leroux, in 1899, 28 cases; and by Cave, in 1901, 3 more, making a total of 31 cases. To this number I am able to add 9 cases that have been seen in Chicago—

1 by Billings, 1 by Billings and Preble, 1 by Preble, 1 by Hektoen, 1 by Quine, 1 by E. F. Wells, and 3 by myself. Raw reports 7 cases from England as seen by himself. Allen and Lull report an interesting primary pneumococcic arthritis of the knee. I have been able to find a few cases also that had escaped the notice of Leroux and Cave. My attention was called to 2 of these by Dr. E. F. Wells, who kindly gave me the references. Altogether I add to Cave's list 21 cases, making a total of 52. In all of these bacteriologic examination has proven the presence of the pneumococcus in the joint. Two other cases I have seen where there is no reasonable doubt as to the nature of the joint affection; but as these cases lack bacteriologic confirmation I am forced to omit them from the series, as also 3 others—2 of Preble's and 1 of Bernheim's.

FREQUENCY. Pneumococcic arthritis is a relatively rare affection. Cave found no recorded observations in England before his, though, of course, cases had previously occurred, but had not been recognized. In running through a number of German inaugural dissertations, most of them statistical studies on pneumonia, I find the following figures:

Name of reporter.	Hospital.	Year.	No. of cases of pneumonia.	No. of cases of arthritis.
Sello,	Urban Hospital, Berlin,	1890–1897	750	One case, right shoulder.
Moosberger,	Zürich (Eichhorst),	1884–1890	359	No case mentioned.
Samter,	Breslau,	1881	331	No case mentioned.
Herrmann,	Leipzig,	1893	235	One case with serous gonitis ("gelenk rheumatismus?").
Fricke,	Göttingen,	1886	169	No case.
Pöhlmann,	Erlangen (Strümpell)	1886–1888	289	No case.
Morhart,	Erlangen (Strümpell)	1888–1892	209	No case.
			2292	2 cases of arthritis.

Vogelius cites the figures of the Charité, in Berlin, for 1874–1889, 3293 pneumonias, with 2 cases of arthritis; Munich, for eleven years, 650 pneumonias, 1 arthritis; several clinics in Paris, 1215 cases of pneumonia, 3 of arthritis.

Netter finds figures of 4156 cases of pneumonia reported from German clinics, with but 6 cases of arthritis. In Allbutt's *System* no mention is made of arthritis as a complication of pneumonia, nor does Aufrecht, in Nothnagel's *System*, refer to it.

These figures and the experience of physicians in general practice

bear out the statement that the complication is quite rare, being found once in perhaps 800 cases; yet, like many other affections, when one is on the lookout for it, it will less easily escape detection, and it will probably be found that its frequency is greater than these statistics would show.

Raw found it in 1 per cent. of his cases. Its frequency in Chicago might excite comment; but most of the Chicago cases referred to in this article were seen in the Cook County Hospital, where many of our pneumonics are also alcoholics—a condition recognized as favoring the occurrence of arthritis, and referred to by Raw as helping to explain his high percentage. We have also in the last few years had a great deal of pneumonia in Chicago of a severe type and presenting atypical and complicated forms; and, as I have said, when one is on the lookout for these things they do not escape notice as they otherwise might.

The following is made up of Cave's table (the first 31 cases), with the additional cases which I am able to add. The first 28 cases are those collected by Leroux. For the sake of completeness I have copied this table entire, and have added the other cases, as Raw has done, with the same order of tabulation of facts as adopted by Cave. The references to the literature of the first 31 cases will be found in Leroux's and Cave's article. I give references, therefore, only for the cases which I have added.

In 47 cases there were 40 males and 7 females. The greater frequency in the male sex may perhaps have a partial explanation in the fact that pneumonia is more frequently seen in males, at least in hospital practice, and that a larger proportion of males would present the favoring influence of previous alcoholism, plumbism, and traumatism, which factors to a certain extent seem to determine the localization of the pneumococcus in the joint. Adding my figures to those of Cave, we have the following facts concerning the age and also the joints most commonly affected. Before ten years, 4 cases; from ten to twenty years, no cases; from twenty to thirty years, 5 cases; from thirty to forty years, 9 cases; from forty to fifty years, 15 cases; from fifty to sixty years, 11 cases; from sixty to seventy years, 4 cases; from seventy to eighty years, 2 cases.

TABLE OF CASES OF PNEUMOCOCCIC ARTHRITIS.

No.	Observer.	Date, sex, age.	Relation to pneumonia.	Seat of arthritis	Nature.	Complications and remarks.	Result.
1	Weichselbaum,	1888 ? 54	Pneumonia, 3 days before.	Right shoulder	Suppurative.	.....	D.
2	Belfanti,	1889 ?	Pneumonia, 11 days before.	Right wrist.	"	.....	D.
3	Monti,	1889 ?	Pneumonia.	Metacarpo-phalangeal.	(?)	.....	D.
4	Ortman and Samter,	1890? M. 34	Pneumonia, few dys. before.	Shoulder.	Suppurative.	Arthrotomy.	R.
5	Macaigne and Chipault,	1891 F. 60	Pneumonia, 4 days before.	Right knee.	"	"	R.
6	Chantemesse,	1891 adult	Pneumonia, crisis 2 d. before	Elbow; knee.	Serous.	Meningitis.	D.
7	Boulloche,	1891 M. 5	Pneumonia, 3 days after.	Knee; both elbows.	Suppurative.	.....	D.
8	Picqué and Veillon,	1891 M. 36	Pneumonia, 4 days before.	Right knee.	"	Arthrotomy.	D.
9	Brunner,	1892 M. 52	Pneumonia, 2 days before.	Left wrist.	"	"	D.
10	Juvigny,	1894 M. 52	Pneumonia.	Both knees; ankle.	"	"	D.
11	Dominici,	1896 M. 44	Pneumonia, 12 days before.	Right shoulder	"	Peri- and endocarditis; meningitis; lead.	D.
12	Griffon,	1896 F. 71	None.	Right ankle.	"	Endocarditis; meningitis; arthrotomy.	D.
13	Mercantonio,	1896 M. 71	Pneumonia, some dys. before	Right shoulder	"	Arthrotomy.	D.
14	Oliva,	1896 M. 8	Pneumonia, 7 days after.	Arms and feet (multiple).	Serous.	Pneumococcus found in sputa only.	R.
15	Vogelius,	1896 M. 38	Pneumonia, 5 days before.	Right sterno-clavicular.	Suppurative.	Arthrotomy.	R.
16	Vogelius,	1896 M. 60	Pneumonia, some dys. before	Hip.	"	Endocarditis; empyema; lead; arthrotomy.	D.
17	Schabab,	1896 M. 45	Pneumonia.	Left hip and knee.	"	.....	D.
18	Ausset,	1896 M. 41	Pneumonia, 7 days before.	Both knees.	"	Rheumatism two years before.	D.
19	Fernet and Lorraine,	1895 M. 56	Pneumonia.	L. sternoclavicular; r. shoulder (recover'd).	"	Endocarditis; meningitis. The arthritis of shoulder subsided before death.	D.
20	Widal and Meslay,	1896 M.ad.	None.	Left first metatarsophalang'l	"	Purulent pericarditis; lead.	D.
21	Duflocq and Ledamany,	1896 M. 32	Pneumonia, 9 days before.	Both elbows; left shoulder; right knee.	"	Old rheumatic arthritis.	D.
22	Tournier and Courmont.	1896 M. 50	Pneumonia, 6 days before.	Left knee and shoulder.	Serous.	Empyema; secondary syphilis.	D.
23	Widal and Mercier,	1897 M. 46	Pneumonia, 4 days before.	Multiple, wrist and ankle.	Suppurative.	Endocarditis; typhoid arthritis 25 years before.	D.
24	Galliard and Morèly,	1898 M. 44	Pneumonia, 9 days before.	Right wrist.	"	Stiffness and grating of joint; arthrotomy.	R.
25	Widal and Lesné,	1898 M. 68	None.	Left sternoclavicular; left wrist.	" (?)	Old chronic rheumatism of small joints of hands and feet.	R.
26	Petit,	1898 M. 42	Pneumonia, 5 days before.	Left knee.	Suppurative.	Meningitis; arthrotomy.	D.
27	Sorel,	1898 M. 48	Pneumonia, 8 days before.	Left shoulder.	"	Empyema.	D.
28	Leroux,	1899 M. 45	Pneumonia, 9 days before.	Left wrist.	"	Endocarditis; pleurisy; peritonitis; meningitis.	D.
29	Fernet and Lacapère,	1900 M. 47	Pneumonia, 3 or 4 dys. before	Right wrist.	Serous.	Joint stiff.	R.
30	Rendu,	1900 M. 66	Pneumonia, 15 days before.	L. sternoclavicular; l. knee.	Suppurative.	Arthrotomy.	R.
31	Cave,	1900 M. 51	Pneumonia, 9 days before.	Left shoulder.	Serous.	.....	D.
32	Nicolaysen,	1896 M. 3 wks	10 dys. from onset of sympt'ms of infectious disease involving bronchi and lungs.	Right elbow.	Suppurative.	Double empyema; suppurative pericarditis; bronchitis; no operation.	R.
33	Mühsam,	1897 M. 55	Entered surg. ward 24 days after onset of pneumonia.	Right shoulder	"	Incision and drainage; desperate case; regarded as hopeless at time of operation; alcoholic.	R.

No.	Observer.	Date, sex, age.	Relation to pneumonia.	Seat of arthritis.	Nature.	Complications and remarks.	Result.
34	Heubner,	1897 5 mos.	At least 3 wks. after onset of pneumonia; several days after normal temperature.	Left shoulder.	Suppurative.	Incision and drainage.	R.
35	Flament,	1898 M. 55	.....	Knee.	"	Resection.	R.
36	Raw,	1898 M 28	Pneumonia, 3 days before.	Right sternoclavicular joint	"	Free incision and drainage; right otitis media and abscess of thigh.	R.
37	Raw,	1899 M. 52	Pneumonia, 2 days after.	Right ankle, right sternoclavicular.	"	Incision, arthrotomy, stiff joint, right empyema.	R.
38	Raw,	1900 F. 49	Pneumonia, 2 days before.	Right shoulder	"	Incision, drainage, arthrotomy, septicemia.	D
39	Raw,	1897 M. 23	Pneumonia, 2 days before.	Right knee.	Serous.	Aspiration.	R.
40	Raw,	1898 M. 51	Pneumonia, 2 days before.	Both knees.	"	General treatment; alcoholism; a severe infection and toxemia.	D.
41	Raw,	1900 M. 58	Pneumonia, 3 days before.	Right knee.	Suppurative.	Incision and drainage; stiff, though fairly useful joint.	R.
42	Raw,	1901 M. 42	Pneumonia, about same time.	Right shoulder	"	General treatment; severe general infection, with extensive cellulitis of shoulder.	D.
43	Billings and Preble,	1899 F. 43	Pneumococcic septicemia; no lung involvm't; pneumococcus from blood, joints, and by lumbar punct.	Elbow, wrist, ankle, knee.	"	Pneumococcic septicemia with localization in pericardium, meninges and joints. Autopsy.	D.
44	Preble,	1899 M. 33	Exact date of arthritis uncertain, but joints swollen at time of first observ. 14 days from initial chill of pneumonia.	Right foot; left knee, elbow, wrist, and second metacarpophalangeal joints.	"	Pneumococci from blood during life.	D.
45	Billings,	1900 M. 23	16 days after chill of pneumonia.	Rt. shoulder, lt. knee, lt. metatarsophalangeal joint of great toe.	"	Meningitis; distinct trauma to joints.	D.
46	Hektoen,	1901 M. 47	.....	Left knee.	"	Pneumococcus in heart's blood at autopsy.	D.
47	Allen and Lull,	1901 F. 40	Primary in joint; no pneumonia, no pneumococcus in the blood.	Left knee.	"	Arthrotomy, and later amputation.	D.
48	Quine,	1902 F. 30	7 days from onset of an angina and 5 from beginning of pneumonia.	Right sternoclavicular.	"	Incision; endocarditis, nephritis, probable pericarditis.	D.
49	Wells,	1902 F. 32	2 days after crisis of pneumonia.	Left sternoclavicular.	"	Incision and drainage.	R.
50	Herrick,	1902 M. 32	7th day of pneumonia immediately following crisis	Left elbow.	"	Aspiration; useful and movable joint.	R.
51	Herrick,	1902 M. 41	15 days from beginning of pneumonia.	Left hip and knee.	Knee, serous; hip, unknown.	Plumber, alcoholic; previous injury of hip and knee; aspiration of knee; useful joint; hip not treated; ankylosis.	R.
52	Herrick,	1902 M. 26	12 days after crisis of pneumonia.	Left knee.	Suppurative.	Incision and drainage; severe toxemic symptoms; pericarditis.	D.

In 23 of the 52 cases the upper extremities alone were involved; in 18 cases the joints of the lower extremities alone; in 11 there was involvement of joints of both the upper and lower extremities. These figures show a slight preponderance in favor of limitation to the upper extremity, but so slight that little or no significance can be attached to it. In fact, the knee seems to be the joint oftenest affected, being involved in 22 of the 52 cases, in 3 of which both knees were affected, so that out of a total of 84 joints the knee makes up 25, or about 30 per cent. The involvement of other joints was as follows: the sternoclavicular, 8 times; the shoulder, 12 times; the elbow, 9 times; the wrist, 8 times; the metacarpophalangeal twice; the hip, 3 times; the knee, 25 times; the ankle, 3 times; the metatarsophalangeal, 3 times. The arthritis was monarticular in 32 instances, or in 61.5 per cent. of the cases. The joints thus solitarily involved were: shoulder, 10 times; knee, 9 times; wrist, 5 times; elbow, twice; sternoclavicular, 4 times; and the hip, ankle, metacarpophalangeal, and metatarsophalangeal each once. Of the remaining cases there were involved two joints, 9 times; three joints, 4 times; four joints, once; more than four, 3 times. These figures bring out the fact that the larger joints—the knee, shoulder, elbow, and wrist—are more often affected than the smaller, though it is to be noted that one of the smaller joints—the sternoclavicular—was inflamed 8 times; oftener, it will be seen, than the hip, which was involved but 3 times.

The influence of trauma in bringing about this form of arthritis has been noted by many writers upon the subject. Five of the number had distinct histories of injury of the joint affected, by sprain or bruise either shortly before or during the course of the pneumonia. One of my patients—Case LI.—four weeks before the onset of the pneumonia had fallen through a trap-door, sprained the knee, which later became infected, and had been for several days confined to the bed on that account. In this connection the case of Billings—Case XLV.—is interesting and instructive. In both these cases the influence of trauma in inducing localization in a given joint seems clear; and, again, it is seen how the arthritis is prone to occur during convalescence.

This production of a locus minoris resistentiæ in the joint by traumatism, thus favoring the localization of the pneumococcus, is in accord with experimental work along this line, dealing not only with this microbe but others, and in connection with such conditions as osteomyelitis, endocarditis, etc. The experimental work in connection with pneumococcic arthritis shows that injection of the pneumococcus directly into the joint, or injection into a vein, the joint being at the same time

injured, frequently results in suppurative arthritis. Subcutaneous injection under similar conditions less frequently results in arthritis. The work of Bezançon and Griffon will be referred to later.

In some cases, too, there has been a history of previous damage to the joints by rheumatism. Lead-poisoning was present in two cases, and in one of these uratic crystals were found in the cartilage of the joint inflamed through the pneumococcus, constituting the point d'appel of Netter. One of my patients was a plumber, though I could not make out any evidence of chronic lead-poisoning; and the man in whom Dr. Hektoen found at autopsy a pneumococcic arthritis of the knee was a painter. Of the influence of the damage to the joint by a mechanical trauma there can be little doubt. Whether previous rheumatism, gout, syphilis, and lead-poisoning also act in this way is less easy of proof, though it would seem to act as a favoring cause in some cases. The possible influence of chronic alcoholism, nephritis, and previous disease in lessening the resisting power of the patient should not be overlooked. In several instances the patients were alcoholics and the pneumonia of the alcoholic type.

For the sake of completeness I give brief abstracts of the cases that I have added to Cave's list.

CASE XXXII. (Nicolaysen).[6]—A boy, aged three weeks, was taken, July 30th, with fever, cough, and rapid respiration. August 9th he cried all night as with pain, and his right elbow was found red and tender, the swelling, later, extending down over the forearm. Death occurred a few days later, and the autopsy revealed a double empyema, suppurative pericarditis, bronchitis, and suppurative arthritis of the right elbow. The pneumococcus was found in the blood during life, and after death was found in the pus in the pleuræ and in the joint.

CASE XXXIII. (Mühsam).[7]—A laboring man, aged fifty-five years, alcoholic, was taken, August 2, 1897, with pneumonia of the right lower lobe. August 31st the right shoulder-joint was opened, and 200 c.c. of thin fluid pus containing the pneumococcus were removed. The joint was much disintegrated. Notwithstanding the serious and seemingly hopeless condition of the patient at the time of operation he made a slow yet permanent recovery.

CASE XXXIV. (Heubner).[8]—A child, aged five months, after a bronchitis and a pneumonia of the upper lobe of the right lung, improved but slowly. No fluid was found on exploratory puncture of the still dull upper lobe. Four weeks from the beginning of the illness the left shoulder became suddenly inflamed, with a rise in temperature. Pus

containing the pneumococcus was obtained on free incision. The child recovered.

CASE XXXV. (Flament).[9]—Flament reported to the Medical Society of Lille, at its meeting of June 22, 1898, the case of a man, aged fifty-five years, who had a suppurative inflammation of the knee following a pneumonia. The pneumococcus was found in the pus. Under resection the patient recovered.

The next 7 cases are those of Raw.[10] I quote his abstracts verbatim:

CASE XXXVI. (Raw).—H. G., aged twenty-eight years, was admitted into Mill Road Infirmary with acute pneumonia of the right lung. The whole lung was involved, and the attack was a very severe one, with considerable pleurisy. He had his crisis on the eighth day, and was apparently doing well, when, on the eleventh day of his illness, he had a rigor, and was seized with intense pain in the right ear, accompanied by a sudden rise of temperature. Next day a swelling appeared over the second right costal cartilage, with great pain and tenderness. Two days afterward a large abscess rapidly formed over the right buttock. His condition became very critical, and his temperature high and erratic. An incision was made over the swelling on the chest, and was found to be an abscess of the right sternoclavicular joint pointing between the first and second ribs; the abscess of the buttock was drained, giving exit to a large quantity of sweet-smelling pus. The abscess in the middle ear burst the same day, giving great relief. Very careful precautions were taken in examining microscopically and bacteriologically the pus from every source above described, as well as the sputum.

In all cases apparently the same organism, the pneumococcus of Fraenkel, was found in pure culture. The man made a good recovery, and is well to this day. I have no doubt that in this case prompt surgical interference saved his life.

CASE XXXVII. (Raw).—T. A., aged fifty-two years, was admitted on January 5, 1900, with severe pain in right side of chest, and profuse, dark expectoration. He had also pain and swelling of right ankle and swelling, with great tenderness, over the right sternoclavicular joint. Next day he was found to have definite pneumonia at the right apex, with effusion at the base.

The joints seem to have swollen before the onset of his pneumonia, and he had suffered from rheumatism on several occasions. As soon as the pus was found in the joints they were freely incised and drained, both articulations being found roughened and bare. The pneumonia ran an ordinary course and his temperature fell, but later he developed

an empyema which was also opened and drained. This man had a most severe general infection by pneumococci, and although repeated cultures were made from the pus and sputum no other pathogenic organisms were found except diplococci. After a long illness he made an excellent recovery, his chest quite healed, as also the sternoclavicular joint; the ankle healed up, but the joint remained stiff.

CASE XXXVIII. (Raw).—K. F., aged forty-nine years, charwoman, admitted June 11, 1900, with severe pain in right chest and abdomen, with all the symptoms of acute pneumonia. She was an alcoholic, and had a severe struggle until the crisis, which occurred on the seventh day. Two days after this a swelling appeared under the right deltoid muscle, with great pain on movement. A needle was inserted into the joint and pus withdrawn. I freely incised the joint, and let out eighteen ounces of curdy, sweet-smelling pus. I noticed at the operation there was considerable infiltration between the muscles around the joint. Her temperature dropped and she appeared to be doing well for twelve days, when she developed empyema of the right side. This was opened and drained; then a large abscess developed in the abdominal wall, which was drained, but the patient sank into a condition of general pyæmia, and died on the twenty-eighth day. Pneumococci in pure culture were obtained in all the samples of pus and sputum.

CASE XXXIX. (Raw).—A man, aged twenty-three years, was admitted with an ordinary attack of acute lobar pneumonia of the right lung. His crisis occurred on the seventh day. Two days afterward he developed a painless swelling of the right knee, with a temperature of 100° F.; a needle drew off clear serous fluid. Under the microscope, however, pneumococci were found in abundance. The joint was aspirated of seven ounces of fluid and firmly strapped. After a slow and tedious convalescence he eventually recovered and walked out with a useful joint.

CASE XL. (Raw).—A man, aged forty-three years, a confirmed alcoholic, was admitted in a collapsed condition with acute lobar pneumonia of the right lung. Two days after admission, being the sixth day of the disease, he developed a painless swelling of both knees. A needle showed serofibrinous effusion which, on cultivation and examination, was found to be a pure culture of pneumococci. He died on the following day, and at the postmortem examination he was found to have a most severe pneumonia, with inflammation of both knee-joints. The organisms recovered from the lung and the knee-joints appeared to be identical.

CASE XLI. (Raw).—A man, aged fifty-eight years, also a drunkard, was admitted on April 13, 1900, with acute pneumonia of the right lung. He had his crisis on the seventh day, and appeared to be comfortable, when he was seized with great pain in the right knee and rapid distention of the joint. A needle showed sero-pus, which on being stained revealed pneumococci with well-defined capsules. Dr. Pitt-Taylor opened and drained the joint, which continued to discharge pus for two weeks and eventually healed, leaving the man a very useful joint. He was discharged, recovered, but his knee was fairly stiff, although not in any way ankylosed.

CASE XLII. (Raw).—F. D., aged forty-two years, tram driver, was admitted on July 12, 1901, with acute pneumonia of the right lung. On admission he complained of great pain in his right shoulder, which was dusky-red and inflamed, but without any definite fluctuation. He died before any operation could be performed, and careful examinations of the fluid from the shoulder showed pure culture of pneumococci. In this case, also, an extensive intramuscular infiltration was found around the shoulder-joint.

CASE XLIII. (Billings and Preble).[11]—A seamstress, aged forty-three years, was taken with chills and became so delirious that she was removed to the Detention Hospital. She was sent a few hours later to the Cook County Hospital, where it was found that she had, in addition to the fever and delirium, a choked disk, a rigid neck and unequal pupils. In the pus obtained by lumbar puncture the diplococcus of pneumonia was found. It was extracellular. The elbow, wrist, knee, and ankle were swollen, red, tender, and painful. From the left wrist a few drops of thick, whitish muco-pus were obtained, showing the pneumococcus; the blood also revealed the same organism. Pericarditis was recognized.

The autopsy (Hektoen) showed pneumococci in the blood, with suppurative inflammation of the meninges of the brain and cord, of the joints, and of the pericardium. The pneumococcus was recovered from each of these locations. There was no involvement of the lung in pneumonia.

CASE XLIV. (Preble).[12]—A male, aged thirty-three years, early in January, 1899, had la grippe. January 23d he had a chill, followed by pain in both sides of the chest, as well as in the right shoulder and all the joints of the left arm. When he came under Dr. Preble's observation he had the evidences of consolidation of the left lower lobe, fluid in the right chest, with some pleural friction. The joints of the right foot, left knee, elbow, wrist and second metacarpophalangeal joint

were red, swollen, painful, and tender. Smears and cultures from the left wrist and from the blood showed only the pneumococcus. Death. No autopsy.

CASE XLV. (Billings).[13]—A male, aged twenty-three years, non-alcoholic, who had several years before suffered from pneumonia and also from rheumatism, was taken ill with severe chill, pain in the left chest, followed by fever, cough, yellowish expectoration changing to rusty. After six days he entered the hospital, where was found a consolidation of a portion of the left upper lobe, the process migrating until the entire left lung became involved. The breathing was rapid, the temperature high, reaching normal by lysis on the ninth day after admission to the hospital and the fifteenth from the onset of symptoms. On this day the patient's mind was clear and he appeared convalescent. Previous to this he had been delirious, and while in this state had jumped from the second-story window to the ground, a distance of twelve or fifteen feet. No bones had been broken, but the right shoulder and left knee were injured. On the day after the temperature reached normal the patient complained of great pain in the right shoulder and the left knee, and the latter was swollen and tender, and fluctuated. The metatarsophalangeal joint of the left great toe was also swollen and tender. Symptoms of meningitis now appeared, and three days later, on the thirteenth day of his stay in the hospital, or the nineteenth from the initial chill, he died. No autopsy. A few hours before death the left knee, right shoulder and spinal subarachnoid space were punctured, each yielding a turbid, purulent-looking fluid that coagulated spontaneously. The fluid from each of these places contained an encapsulated diplococcus that stained by Gram. In cultures the growth was typical of the Fraenkel diplococcus.

CASE XLVI. (Hektoen, personal communication).—The clinical history is lacking. The patient was a male, aged forty-seven years, by occupation a painter. The anatomic findings showed a lobar pneumonia of the upper and lower lobes of the right lung, acute bronchitis of the left lung, and a purulent synovitis of the left knee-joint. This joint contained a large quantity of thick, creamy pus. The synovial membrane was swollen and reddened, but there were no erosions in any part of the joint. The right knee-joint was normal; smears from the lung, the heart's blood, and the pus in the joints revealed a diplococcus staining by Gram. Cultures from the pus gave a diplococcus staining by Gram and identified as the diplococcus of pneumonia.

CASE XLVII. (Allen and Lull).[14]—A woman, aged forty years, was taken with cramps in the abdomen and pain in the left knee. Rheu-

matism and then gonorrhea were suspected. No further facts as to her history were obtainable. The urine was negative. The leukocytes, 27,000. On the fifth day the joint was distended, tense, and very painful. The temperature varied from normal to 101° F. The joint was freely opened, irrigated and packed, thick yellowish pus containing only the pneumococcus being evacuated. The temperature rose, and the next day the patient was delirious. An amputation was made in the lower thigh, well away from the joint and through apparently healthy tissue. There was some temporary improvement, then pus appeared in the wound; there were leukocytosis, chills, and death, with a temperature of 108.2° F. Death occurred seventeen days after the first symptom.

Autopsy (Dr. W. T. Howard) showed the pneumococcus and the staphylococcus pyogenes aureus in the amputation stump, with interstitial myositis and suppuration. No germs were found in the blood or in the heart, lung, liver, spleen, or kidneys. Death, therefore, seemed to be due to toxemia, and the primary joint infection had arisen through some unrecognized portal of entry of the pneumococcus.

Case XLVIII. (Dr. William E. Quine, personal communication).—The patient was an anemic, overworked young woman of exemplary habits. Early in February, 1901, she was ill with rheumatism, which had nearly disappeared, when, on March 5th, she had a hard chill, high fever, and a severe sore-throat resembling a phlegmonous inflammation. No pus was found on puncturing the tonsil, but a nearly pure culture of the pneumococcus was obtained from the throat. Other chills followed, and signs of pneumonia of the lower lobe of the right lung appeared, with evidence of an acute endocarditis. There was a suspicion also of a pericarditis. The urine contained albumin, casts, and a microscopic quantity of blood. March 12th the patient was in a nearly moribund condition. A swelling was at this time noticed over the right sternoclavicular articulation. How long it had been forming is not known. Two drams of thick pus were evacuated, which pus contained only the pneumococcus. The patient died a few hours later.

Case XLIX. (Dr. E. F. Wells, personal communication).—A lady, aged thirty-two years, was taken, January 17, 1898, with a chill, followed by fever, pain, cough, expectoration, and all the ordinary symptoms and signs of pneumonia of the lower lobe of the right lung. The attack was one of moderate severity, with a temperature ascending to 104° F., respirations to 32, pulse to 124, and leukocytosis to 24,000. There was no delirium, but after the first three or four days there was noticeable pallor. On the sixth day there were, for several hours, pain

and tenderness along the course of the left femoral vein. On the seventh day the temperature began to decline and reached the normal point on the following morning. The pulse, however, remained well above 100, and the patient felt weak and tired. On the morning of the ninth day the left shoulder was reported as sore and painful when moved. In the evening a small, tender swelling was discovered over the left sternoclavicular articulation, which, on the next day had increased to the size of a large hickory-nut, and was reddened and softened. This was incised, giving exit to about three drachms of greenish-yellow pus. The cavity was washed out with peróxide of hydrogen. A seropurulent discharge continued for three or four days, when it ceased and the wound closed, without further symptoms. The pus contained only pneumococci, which were stained by Gram's method. Cultures, also, showed only the pneumococcus. Recovery was perfect, but convalescence was unusually tedious. It is interesting to note that the pain was referred, indefinitely, to " the shoulder," although there was no evidence that this joint was affected.

Case L. (Herrick).—Thomas L., single, aged thirty-two years, laborer, came under my care in the Cook County Hospital, April 10, 1898. His mind was clear, and from him were obtained the following facts: There was no hereditary taint, though several brothers and sisters had died young, the exact cause of death being unknown. The patient had been a free user of beer and whiskey. He had had gonorrhea and a soft chancre, though no fresh venereal disease for more than two years. He had regarded himself as in good health until four days before, when, after an ordinary " cold," he had a slight chill, began to cough more, and noticed pain in the right axilla. He at once quit work.

On examination the typical physical signs of consolidation of the upper and middle lobes of the right lung were found, the dulness and bronchial breathing, with a few fine moist râles, being accurately limited to this area. The heart and other organs revealed nothing abnormal except that the urine contained a moderate amount of albumin and a few hyaline casts. Its specific gravity was 1021. There was slight icterus. For three days the respiration was rapid, 36 to 50; the pulse varied between 96 and 144, and the temperature from 101° to 104.3° F. On the morning of the seventh day of the illness the temperature was 98° F., and from that time on there was a gradual improvement, though it was not until April 19th, the thirteenth day, that the evening temperature did not rise above 99° F. At this date the breathing was 30, pulse 84; the patient still quite weak. The

treatment was by large doses of digitalis, after the method of Petrusco. April 14th, the seventh day of his illness and on the morning of which the temperature was 98° F., the following note is recorded: "Since morning the patient has been complaining of pain in the left elbow, and keeps the left arm quiet. The left elbow is swollen, reddened, tender to pressure, and extremely painful on motion. There is considerable edema, especially over the external aspect of the joint. There has been no extension of the pneumonic process in the lungs. The heart tones are normal, though the action is rapid and the pulse is rather weak. The urine still contains some albumin." Hot boric-acid dressings were applied to the joint. April 20th there was slight fluctuation; and in the clinic, under aseptic precautions, I withdrew by means of an aspirating syringe about two drams of a yellow, creamy pus. I withdrew all that I could. Smears were made at once, and showed a diplococcus morphologically like the diplococcus of pneumonia. Further examination of the pus by cultures showed the organism to be the diplococcus pneumonia. No other germs were found. Several specimens of sputum taken at different times during the course of the disease revealed abundant diplococci, but no tubercle bacilli. The joint showed immediate improvement after the aspiration, and from that time there was a gradual return to the normal condition of the elbow. When the patient left the hospital, May 16th, there was no redness or swelling, and but slight pain on firm pressure over the joint. The motion of the elbow was free. On the date of discharge the patient's lung had cleared up, and he was rapidly regaining his strength.

Case LI. (Herrick).—John H., white, aged forty-one years, married, a plumber by trade, enjoyed good health since childhood. He denied syphilis, and had had no sign of gonorrhea since an attack ten years ago. He had never had any manifestation of lead-poisoning; had indulged rather freely in alcoholics. His father died of pneumonia; his mother and one sister of phthisis.

August 15, 1900, he fell through a trap-door and sprained his left knee, causing great pain and some swelling, and making him drag his leg for a few days. By September 1st he felt all right, and regarded himself as recovered. He then began drinking heavily, and suffered from vomiting, diarrhea, and some pain on the inner side of the thigh. The history here is rather vague, as the patient was under the influence of liquor most of the time; but he remembers some pain in the thigh, some swelling of both legs, and the vomiting. He was kept in bed by a doctor for a time.

September 18th he began to cough, and had pain in the chest, with

fever. He was sent to the Cook County Hospital, where he came under my care September 21st. He was nervous, sleepless, soon delirious, had a coarse tremor. There were dulness, bronchial breathing, and a pleural friction over the lower left chest. The heart was normal as to size and sounds, and was not displaced. The examination of the abdomen revealed nothing abnormal, as also did the examination of the genitalia and lymphatic glands. There was some edema about either ankle. The urine contained a trace of albumin, but no casts. The temperature for a week ranged from 100° in the morning to 103° F. in the evening; the respirations rose to 40; the pulse averaged 130. The patient ran the course, for a week, of an alcoholic pneumonia, and was seriously ill. He became rapidly emaciated, and, the fever not disappearing by crisis, tuberculosis was suspected. Several examinations of the sputum failed to reveal tubercle bacilli, however, and the lung gradually cleared up. On September 27th a to-and-fro friction rub was heard over the precordia, thought to be pericardial. It disappeared in twenty-four hours.

October 3d the pulse was 110, respiration 30, temperature 100° F., the lung clearing. On this day he complained of quite severe pain in the left hip and knee. He lay with the thigh partly flexed on the abdomen; no local swelling could be made out in either joint. This pain continued with varying intensity, and was relieved somewhat by hot fomentations and later by extension by a weight and pulley. No local redness, swelling, or edema could at this time be made out in either the hip or the knee. The temperature remained for four weeks between 98° and 99.8° F.

By November 27th, after the extension had been discontinued for several days, and when the hip showed very limited motion, and this very painful, the left knee had become decidedly swollen and fluctuated. By aspiration 30 c.c. of slightly reddish, thin fluid was withdrawn. A second aspiration was made nine days later and 15 c.c. of a similar fluid withdrawn. The fluid from the joint contained in smears an encapsulated diplococcus staining by Gram, and in cultures was identified as the diplococcus pneumoniæ. The knee was bandaged tightly, and the patient left the hospital December 27, 1900, using a crutch.

In September, 1901, I sent for him to come to my office, and I found him in good general condition, with normal heart, lungs, and abdominal organs. The urine was non-albuminous. There was no blue line on the gums. The left knee was freely movable, and appeared normal in every respect except for a very slight tenderness. The left hip, how-

ever, was fixed, though painless. With every movement the pelvis was tilted, and a seeming shortening of the left limb was found by careful measurement to be apparent rather than real, and due to a tilting of the pelvis. There was no patellar reflex on the left side; it was present on the right. The left thigh was smaller in circumference than the right by three inches; the left leg measured twelve inches, the right twelve and a half. The man walked with a cane, was free from pain, and was ready to do light work. The muscular atrophy and loss of the patellar reflex in the affected limb suggests the possibility of a simultaneous involvement of nerve and joint, or the nerve or the muscle may have been inflamed secondarily. In several autopsy records the muscle has been described as involved in the pneumococcic inflammation. Bezançon and Griffon make the statement that in their experimental work they were struck by the absence of muscular atrophy in the vicinity of the joint, a fact "not in accord with what has been observed in man." Further observations on this point would be interesting.

Case LII. (Herrick).—Walter F., aged twenty-six years; single. Family history negative. December 9, 1901, when in apparently good health, suffered from earache. That night he had a temperature of 103° F., and on the following day was told by his physician that he had pneumonia. There were no chills and no pain in the side. He coughed, but the sputum was scanty. The temperature ranged between 102° and 104° F. December 14th he became delirious, and the next day was brought to the Presbyterian Hospital, and from that time on was under my care.

He was a well-developed and well-nourished man of medium size; was quite delirious. Over the left lower lobe were dulness, bronchial breathing, and increased voice sounds as in croupous pneumonia. A pericardial friction rub, to and fro in character, was best heard in the right third interchondral space. The respiration for three days was between 40 and 50, the pulse 110 to 136, the temperature 102° to 104.6° F. The urine showed some albumin and a few hyaline and granular casts. On the evening of December 17th the temperature fell by crisis, and was practically normal for five days. During these five days the respiration was easy and regular, 28 to the minute, the pulse was never over 90, the mental condition was one of brightness, and the local signs were those of slow resolution.

December 25th he complained of earache, and that night his temperature rose; no new local changes could be made out in the lung, nor was anything abnormal discoverable on examination of the ear, Dr. W. T. Montgomery kindly making this examination for me. The patient's

general condition became steadily worse, the mind becoming dull, the tongue dry, the pulse rapid and quick, even to 144, and the temperature never below 103° F., and often nearly 106° F.

The case looked like one of severe septicemia. An examination of the blood, four drams being taken from the right median basilic vein, showed no growth on agar plates. December 29th he complained of pain in the right knee. Examination showed very little tenderness to pressure, no redness, but a little fulness, particularly at the inner side of the patella. There was a suspicion of fluctuation. The next day there was more swelling and distinct fluctuation. Exploratory aspiration revealed a thick, creamy, yellow pus. The joint was opened and drained by Dr. D. W. Graham, two ounces of pus being removed. At the same time the left elbow was opened because of redness and tenderness, though no pus was found. No drainage tube was here inserted. There was no improvement in the general condition, which was one of high temperature, rapid, often uncountable pulse, dry tongue, delirium subsultus, involuntary evacuations—in a word, that of a pronounced septicemia or toxemia. Death occurred early on the morning of January 1, 1902.

No autopsy was to be obtained, but the house physician, Dr. Loomis, immediately after death made a puncture of the pericardium, drawing off about two ounces of reddish-yellow fluid, which showed no growth in cultures. Blood from the heart also showed no growth on bouillon, gelatin, and blood serum. The original pus from the puncture of the knee showed in smears an organism in pairs or short chains, the individual organisms varying somewhat in size, the majority being small and somewhat elongated. It stained by Gram's method; no capsules were seen. About ten drops of the pus were injected into the ear vein of a rabbit, but beyond producing a local reaction resembling a dry gangrene there was no result. Cultures on agar, glycerin-agar, bouillon, gelatin, and potato showed reactions that were identical with those of the pneumococcus. Unless transplanted every few days it quickly died out. Cultures from four agar tubes from two to four days old were scraped up, suspended in bouillon, and injected into the posterior ear vein of the same rabbit one week after his first injection with the pus. The animal appeared quite sick inside of twenty-four hours, but recovered. Its failure to cause death of the rabbit may have been due to a lack of virulence, or, in the first inoculation experiment, to the small dose employed, and, in the second, to the partial immunity resulting from the first inoculation.

I have seen two other cases of what were, I am quite sure, pneumo-

coccic infection of a joint during the later days of a croupous pneumonia. As no cultures were made, however, the crucial proof is lacking. The first concerns a female child, aged two and a half years, who ran a typical course of croupous pneumonia, with involvement of the right lower lobe. Crisis on the tenth day. The next day the child cried whenever the left foot was touched, as in bathing. Over the tarsus, just below and in front of the external malleolus, was an area of redness, swelling, and extreme tenderness that appeared to involve a tarsal joint. There was no elevation of temperature. The lung was rapidly clearing. The heart valves were normal. In three days I was sure there was fluid, and urged consultation with a surgeon. This was flatly refused by the parents, who feared an operation and consented to take all responsibility for the non-surgical treatment of the trouble in the foot. In my own mind I was convinced that surgery would be necessary; but, to my surprise, after ten days there was distinct lessening of all evidence of inflammation, and in the course of three weeks the swelling and redness had disappeared. In six weeks the child was up and walking about without a limp.

In a second case, an adult male, the day after the crisis of an alcoholic pneumonia, complained of severe pain over the outer side of the right foot, where were seen some redness and swelling. Movement of the foot and pressure caused great pain, the inflammation seeming to be in one of the tarsal joints. That night the patient had a convulsion, became delirious, had retraction and stiffness of the neck, with sharp rises of temperature, and died with the manifestations of an acute meningitis. No autopsy was permitted. Here, apparently, was a pneumococcic infection of the joint and of the cerebral meninges due to pneumococcic septicemia, with metastatic localization in the joints and the meninges.

In adding these 21 cases to the list I follow the rule that Leroux and Cave have adhered to, with the single exception of Oliva's case, and include only such as were proved by direct examination of the fluid to contain the pneumococcus in the joint. Five other cases were, in all likelihood, of the same nature, and might, without straining one's conscience very much, be added to the list. Two in my own practice I have already alluded to. One case is referred to by Lippmann[15] as reported by Bernheim—an old rheumatic alcoholic with a double pneumonia, suppuration in the left scapulohumeral joint, meningitis, and death, the autopsy revealing vegetative endocarditis. Two of Preble's cases could also be safely classed here. The one concerned an adult male, who, several days after recovery from typhoid fever and erysipelas, had a right upper lobe pneumonia, with arthritis of right knee and left

shoulder, with several abscesses of the soft parts. No cultures were made from the joints, but from an abscess of the back and from one of the scrotum the pneumococcus was recovered. The patient died, and no autopsy was permitted. His second case was in a child, aged fourteen months, with pneumonia of the left lower lobe. On the third day a swelling of the left hand appeared, with swelling and redness of several of the small joints. Pus from a periosteal abscess over the external condyle of the humerus revealed the pneumococcus. Later, other abscesses in the soft parts appeared, as did an otitis media, and there was a relapse of the pulmonary trouble. Ultimately recovery ensued.

Symptomatology. The clinical manifestations may be briefly described as those common to all acute inflammations of joints. The frequent occurrence of this complication during convalescence from pneumonia, at a time when the patient's mind is clear and the attention of the physician is not attracted too particularly to the lung, causes the complaint of local pain to be recognized by the patient and heeded by the physician. The pain varies in severity from that which is slight and has come on gradually to that which is of extreme severity and of abrupt onset. The tenderness is usually pronounced. The joint becomes rapidly or gradually swollen, and when the accumulation of fluid is great, fluctuation can be detected. There is also, in many cases, periarticular involvement. Redness, superficial tenderness, and wide-spread edema may show that the inflammation is not confined to the joint proper, but involves as well the structures about the articulation. The appearance of the joint in these cases is not unlike that seen in many cases of gonorrheal arthritis, and the resemblance is the more striking when we remember the tendency of each of these forms of arthritis to attack the larger joints, only one or a few joints at a time, and for the inflammation to be permanent and not shifting from one joint to another. The periarticular edema is more likely to be pronounced in the cases with a subacute course. Here, as shown by clinical and experimental observation, there is greater destruction of joint structures and greater invasion of surrounding tissues.

As regards the diagnosis in the cases with much periarticular swelling, it is to be remembered that the inflammation and the resulting abscess may be near or about the joint, and yet not involve the joint proper. Such periarticular localizations of the pneumococcus have been reported by Gabbi and Puritz.[16] Netter also refers to them. And in the County Hospital recently an autopsy was made on a patient in whom the pus was found to be not in the joint, as had been suspected

during life, but in the subdeltoid bursa—a localization referred to as common by Netter. This case—one of Dr. Preble's—was an instance of a croupous pneumonia, with the abscess containing a pure culture of the pneumococcus. In the child with the abscess on the side of the foot—the case which I regarded as involving the joints of the foot—it is possible that the joint itself was not invaded, but that the abscess was periarticular.

The occurrence of an arthritis during the course of a croupous pneumonia, and especially during convalescence from the same, would naturally lead to the suspicion of a pneumococcic inflammation; and color would be lent to this supposition if the patient were an alcoholic or if his affected joint were the seat of a previous trauma or injury from rheumatism or gout. But an arthritis complicating pneumonia need not be due to the pneumococcus. Other organisms may enter the circulation and lodge in the joint. This point is well brought out by Mauclaire,[17] who quotes Smirnow[18] as finding in ten cases of pyarthritis complicating pneumonia five in which were found organisms other than the pneumococcus, such as the typhoid bacillus, the streptococcus, and the staphylococcus. It becomes necessary, therefore, to make an exploratory puncture of the joint, and, by smears, culture, and inoculation, to determine as to the presence of the pneumococcus and its degree of virulence. The existence of fluid and its character is thus determined in doubtful cases—a fact of no slight importance from its influence on prognosis and treatment.

Cases of single or multiple painful joints during or following pneumonia are referred to by Netter, who has seen several. In some of these slight local swelling is seen; in others the affection seems to be little more than an arthralgia. Spontaneous recovery seems to be the rule.

The constitutional symptoms show great variations. In many cases the symptoms due to the bacteriemia, or to the involvement of some important structure like the pericardium, pleura, or meninges, completely dominate the picture, and the joint symptoms seem wholly insignificant by comparison. High fever, rapid pulse, dry tongue, delirium—in a word, the clinical picture of a severe septicemia—are present. Apparently, too, this can be present without true bacterial invasion of the blood, as the case of Allen and Lull seems to show, where toxemia seemed to be the cause of the profound and fatal constitutional disturbance; and in my own case (Case LII.), though no autopsy was made, the examination of the blood during life did not reveal organisms, though the symptoms were of the most virulent type. In other cases

the constitutional symptoms are relatively slight, except that the patient is weak and exhausted from his pneumonia, and makes but a slow convalescence. The joint involvement, when subacute in its course, may have but a slight influence on the temperature or pulse.

PROGNOSIS. The prognosis is, from the nature of things, grave. The primary lung involvement is in itself serious, and the arthritis implies, at least in most cases, a bacteriemia, with the probability of other metastatic foci of inflammation. The combined toxemia and involvement of other structures often more vital than the joints—*e. g.*, the pleura, meninges, endocardium, or pericardium—must make the prognosis grave. Of the 52 cases 34 died and 18 recovered—a mortality of over 65 per cent.

TREATMENT. That pneumococcic infections of other structures are often relatively benign is well known. The prognosis in a pneumococcic empyema is better than where the trouble is due to the streptococcus. The treatment in these cases might, therefore, be less radical than in other cases of pyarthritis. Where, however, the fluid is purulent it would certainly seem wise to incise at once and drain the joint. It would seem to me questionable, however, whether several incisions, with numerous drainage tubes or gauze drains, with free irrigation—in other words, whether too much manipulation of the joint—is advisable. In many of the acute and most virulent forms there are no solutions of continuity in the synovia or cartilage; the coarse insult to the joint from a radical and unusually thorough operation may be the means of causing local spread of the inflammation or of opening up more freely channels of absorption, so as to aggravate rather than ameliorate constitutional symptoms. There seems to be a general agreement among surgeons that a pleural empyema due to the pneumococcus is best treated by incision and drainage, without much disturbance of the pleura even by irrigation. May not the same be true of a joint?

In one of my cases (Case L.) a simple aspiration of the elbow-joint, with the removal of all the pus that could be withdrawn, resulted in recovery. Widal and Lesné[19] removed two drops of pus for diagnostic purposes from the sternoclavicular joint of their patient; a week later two more drops, the fluid this time seropurulent. Recovery followed in six weeks, which recovery may be called, as they themselves term it, spontaneous. These were cases in which thick, creamy, yellow pus was present. In several cases spontaneous recovery has followed where a thinner fluid, seropurulent or serofibrinous, has been present. In my case (Case LI.) recovery with a good joint followed the removal by two

aspirations of a serofibrinous fluid. Netter says that even where there is redness, swelling, and exudate the lesion is susceptible of recovery by simple medical treatment of immobilization and compression. Raw had a recovery by aspiration.

While, therefore, the prognosis, for the reasons above stated, must always be uncertain and generally grave; and while, with pus in the joint, an early, free incision is to be advocated, it is well to remember that with serous exudate, and in a few cases even with purulent exudate, recovery has ensued either spontaneously or by the simpler measures of rest, compression, or aspiration. And we believe that in the arthrotomy, which should be done early when it is indicated, there should be as little damage as possible to the joint structures by unnecessary manipulation.

Pathology. The pneumococcus reaches the joint through the blood-current. The joint is occasionally primarily involved. Five of the reported cases are of this character. In one—that of Allen and Lull—there was no other part of the body infected, nor did the blood, post-mortem, reveal the pneumococcus. This would seem to show the great importance of toxemia in such cases, this particular one being attended by unusually severe and even fatal constitutional symptoms.

The factor that determines the involvement of a particular joint is not always clear; yet experimentally it has been shown that a joint previously damaged is far more likely to be the seat of the local action of the pneumococcus when it is injected into the blood than one that has not been injured. (Gabbi, Ausset, Zuber.) Clinically, the occurrence of pneumococcic arthritis in joints recently sprained or bruised is so common as to excite comment of all observers and to be looked upon as more than accidental. Joints the seat of rheumatic, gouty, or saturnine damage are, according to some, especially prone to this form of arthritis.

A point of interest, and one not easy of an entirely satisfactory explanation, is the fact that this form of inflammation is especially prone to appear after the crisis of the pneumonia and when the patient seems past danger and well on toward convalescence and presumably immune The experimental work of Bezançon and Griffon[20] is in accord with these clinical facts. While working on problems of immunity, and while vaccinating rabbits against pneumococcic infection it was discovered almost by accident that suppurative arthritis occasionally appeared long after the injection of the microbe, and they concluded that pneumococcic arthritis is more likely to appear when inoculation is made with a culture that is attenuated through age, or when inocula-

tion is made with a large dose—a brutal dose—of a virulent culture, but the animal rendered relatively immune by previous vaccinations. Possibly, as has been rather imaginatively expressed by Lippmann, the germ of feeble power having broken into the general circulation is unable to produce a generalized infection, is repelled on all sides, by the other stronger tissues and finally ensconces itself on the serous articular surfaces that are less able to defend themselves than other parts of the body. Leroux calls attention to the fact that this articular localization of the pneumococcus during convalescence from pneumonia is but an exemplification of a general pathologic law that microbes of attenuated virulence are prone to lodge readily upon the various serous surfaces and especially upon the articular surfaces of the joints, and that it accords with the clinical observation that the articular determination of infectious diseases appears chiefly during the period of convalescence.

The changes that occur in the joints vary largely with the duration of the inflammation, and also undoubtedly with the virulence of the micro-organisms, as well as the resisting power of the body in general, and in particular the joint structures. In the acute cases often little more is seen than a synovitis, with redness and swelling of the synovia, and the ordinary histologic changes of an inflammation of a serous membrane. The exudate varies from a serous or serofibrinous fluid to the more commonly found thick, creamy, yellowish pus, which contains the pneumococcus. In the same patient one joint may contain a purulent and another a serous exudate. In other cases, and particularly those of a subacute or more chronic character, the changes are more extensive and destructive. The cartilage may be eroded, the bone invaded, the ligaments destroyed, the tendon sheaths and muscles in the vicinity of the joint involved, so that the inflammation is a periarthritis as well as an arthritis. The destruction may be extreme as in the case—and that an acute one—of Fernet and Lorraine.[21] Here the autopsy showed that the left sternoclavicular joint did not in reality any longer exist. The periarticular fatty tissues were infiltrated with serum, the muscles were disintegrated and marked with streaks of pus, the ligaments, the synovial membrane, the cartilages were destroyed and the articular surfaces were represented on the side of the clavicle, as well as of the sternum, by rough, denuded bone, exposing the spongy portion. Strange to say, there was a minimum amount of pus in the joint cavity, though a virulent pneumococcus was found. In the cases of longer standing attempts at regeneration are made, and healing may occur, with more or less deformity from bony outgrowths and from the

adhesions of scar tissue. The functions of the joint may, of course, be more or less interfered with in this way. In a rabbit that was killed seven months from the injection of the pneumococcus and six months from the first sign of lameness, the appearances of the joint reminded Bezançon and Griffon of an old fracture with vicious union and exuberant callus.

Conclusions. From my study of, and experience with, arthritis due to the pneumococcus, I would agree with nearly all of the conclusions reached by Leroux, some of which are here practically repeated:

1. It is a rare affection, found oftener in men, sparing no age.

2. It appears oftenest during or shortly after croupous pneumonia, sometimes as late as the third week after the crisis.

3. It may be primary in the joint, and severe and even fatal constitutional symptoms may result from the toxemia thus induced; in these cases of primary pneumococcic arthritis pulmonary localization may or may not occur.

4. Previous damage to a joint as by trauma, rheumatism, or gout favors the localization.

5. The lesions may be limited to the synovia or may be more extensive, involving the cartilages and bones. The periarticular structures may be involved. The subacute cases are sometimes highly destructive to the joint, and the same is true of some of the acuter ones.

6. The lesions are usually monarticular (61.5 per cent), the larger joints being oftenest involved. The knee is the joint most frequently affected. The joints of the upper extremity are affected a little oftener than those of the lower, but the difference is insignificant.

7. The condition is recognized by the ordinary signs of an acute or chronic inflammation of a joint. Exploratory aspiration, with bacteriologic examination of the fluid, is the only means of recognizing the pneumococcic nature of the inflammation. The gonorrheal arthritis and periarthritis have to be carefully excluded, as well as the arthralgias following pneumonia.

8. The prognosis is grave—mortality 65 per cent.—largely because of the accompanying bacteriemia and involvement of other more vital parts of the body (meninges, pleura, pericardium, etc.). Yet spontaneous recovery occasionally follows, even where there is a purulent exudate.

9. The cases of suppurative pneumococcic arthritis should be treated by immediate incision and drainage. Serous arthritis may often be healed by aspiration, rest, and compression.

As this paper is going through the press there appears in the *Jahrbuch für Kinderheilkunde*, April 5, 1902, an article by Pfisterer, of Basel, on the same subject. Pfisterer adds several cases seen in children. He does not, however, refer to the monograph of Leroux, by all odds the best article yet written upon the subject.

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DISCUSSION.

Dr. Osler: This subject has interested me very much, as it has been recently worked up carefully by one of my assistants. It appears that there are three groups of cases: one with a local arthritis; secondly, the arthritis following or associated with pneumonia, and, thirdly, an arthritis associated with a general pneumococcus septicemia. I would like to refer briefly to a case of the latter kind. On my visit to the hospital one morning I found in the colored ward a man of uncertain age, who had been admitted the evening before. Three days previously he had a severe chill. On admission he was

semicomatose and could give but little account of himself. He had a swelling of his knees and ankles, and this we learned from his wife had existed for some time. There was some stiffness of his neck, and lumbar puncture showed a turbid fluid from which diplococci were obtained. Blood cultures showed numerous pneumococci, as did also aspiration of the joints. He died on the fifth day of his illness, and we found very extensive pneumococcus meningitis, arthritis, and general infection of the blood. In this case it was difficult to say which was the primary lesion.

DR. MUSSER: I have had under my care during the winter a similar case of that group. Following an attack of pneumonia the patient had an involvement of the joints beginning at the sternoclavicular junction. He was desperately ill, but finally recovered.

PROGNOSIS AND TREATMENT OF TUBERCULOUS PERITONITIS.

As Based on the Experience of the Massachusetts General Hospital for the Past Ten Years.

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"The termination of tuberculous peritonitis is always fatal, either from the disease itself or from tuberculosis of the lungs or other organs. The duration is from one or two months to a year or more." So said Austin Flint in his *Practice of Medicine*, and, curiously enough, the editors of the editions which have appeared since Dr. Flint's death seem to have overlooked this statement and have left it unchanged. We now know as well as we can know almost anything in medicine that tuberculous peritonitis not infrequently gets well. For this important increase in knowledge we are indebted indirectly to Ephraim McDowell, who blazed the path to the operative treatment of ovarian disease. Spencer Wells operated on a young woman, the subject, as he supposed, of an ovarian cyst. He found the peritoneum universally studded with miliary granules resembling those of tuberculosis, sewed up the belly as fast as he could, and, to his surprise, the patient recovered, afterward marrying and becoming the mother of a family. Other ovariotomists had similar experiences, and thus cut the ground from under the feet of those who maintained that recovery from tuberculous peritonitis was proof of an error in diagnosis.

Thus modern surgery proved the curability of tuberculous peritonitis, not the least of its services to humanity.

The next step from the demonstration of curability by surgical intervention to its curative action was a wholly natural one, and attempts were, of course, made to explain how the action is curative. None of these explanations are really explanatory, as far as I know. Flint's statement is doubly inaccurate, for not only is tuberculous

peritonitis not always fatal, but the subject may recover if parts or organs other than the peritoneum are also involved in the disease.

For some time the evidence has seemed to warrant the belief that somehow surgery may cure when all other treatment fails. The wish to obtain guidance as to which cases are adapted to medical, which to surgical, treatment; when to abandon medical for surgical treatment —the hope that I might secure more fixed therapeutic principles, useful to myself and possibly to others—led me to the following analysis of the medical and surgical records of the Massachusetts General Hospital for the past ten years. For this opportunity I wish here to thank my colleagues on the hospital staff; for indispensable and laborious assistance Dr. W. H. Smith, of Boston. The amount of work involved in such an investigation, especially when end-results are sought from hospital patients, is fully appreciated only by those who have personally pursued it.

From 1889 to 1900 there have been 98 cases of tuberculous peritonitis treated at the Massachusetts General Hospital, either on the medical or surgical side. An attempt has been made to ascertain the end result in as many of these cases as possible. Including those patients who were discharged dead, and those in regard to whose condition replies have been received, the end-result is known in 57 cases, or in 58.1 per cent. In the cases included in this series the shortest time which has elapsed since the patient left the hospital is two years, the longest eleven years.

The more important facts in regard to these cases may be of interest, as serving to show the character of cases which have made up the series.

Age.		*Age.*	
From 1 to 5	6	From 40 to 50	5
" 5 " 10	7	" 50 " 60	1
" 10 " 15	8	" 60 " 70	2
" 15 " 20	17		—
" 20 " 30	39		98
" 30 " 40	13		

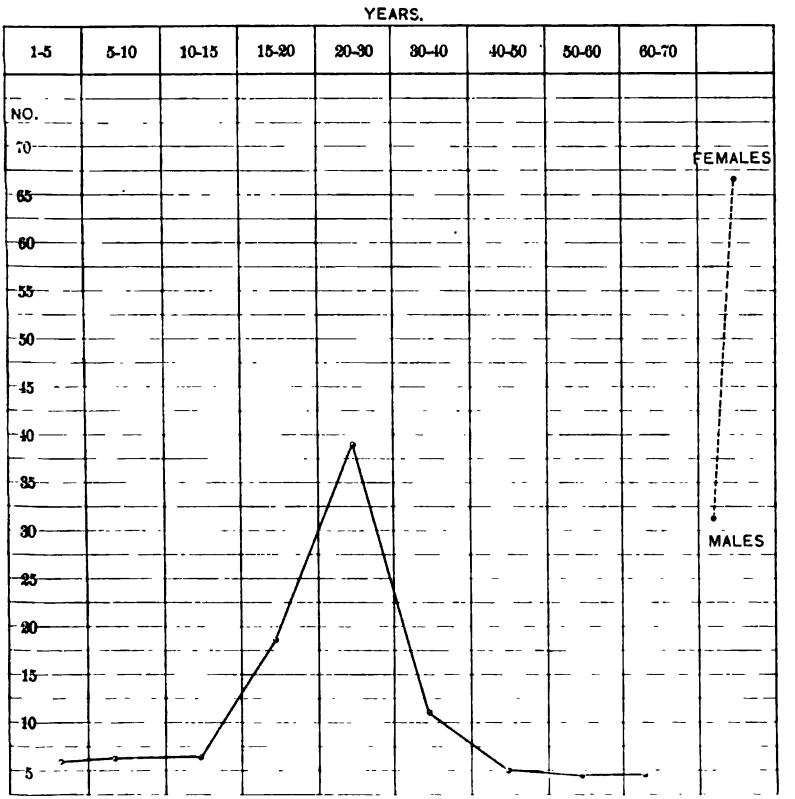
Between the ages of fifteen and thirty years there were 56 cases, or 57.1 per cent. of the whole number. The youngest case was thirteen months; the oldest case was sixty-two years.

The above list does not fairly represent the frequency of the disease in childhood, as the number of children entering the Massachusetts General Hospital is relatively small. In 1889 the number of children admitted was 43, the number of adults 3419. In 1899 the number of children admited was 348, the number of adults 4468. Speaking

broadly, the number of children admitted during the years 1889 to 1900 averaged about 4 per cent. of the total number admitted.

Americans	62
Foreign	31
Not stated	5
	98
Number of males	31
Number of females	67
	98

Included in this number were six of the colored race.



Family History. The presence of tuberculosis in the family history is recorded as follows:

In 2 cases the mother died of phthisis; in 7 cases the father died of phthisis; in 2 the father died of lung trouble; 1 had one brother die

of phthisis; 1 had two brothers die of phthisis; 1 had two aunts die of phthisis, and 1 had one aunt die of phthisis; 1 had a mother and sister, and 1 a mother and brother die of phthisis; 1 had a sister and brother die of hydrocephalus; 1 had a mother die of phthisis and a sister of meningitis; 1 had a father die of fistula in ano; 1 had a husband die of phthisis; in 20 cases there seems to be a distinct history of tuberculosis in the family. In 1 association with a tuberculous husband was recorded.

Previous History. With our present belief in the possible tubercular origin of many if not most of the primary pleurisies, it has seemed best to note a previous attack of pleurisy when stated: One pleurisy, eight months previous; 1 pleurisy, seven years ago; Pott's disease three years ago; 1 pleurisy, eleven months previous; 1 pleurisy, one year ago; 1 pleurisy, three years ago; 1 pleurisy, seven years ago, repeated attacks since; 1 pleurisy, eleven months previous; 1 pleurisy, one year ago. The record states that 3 of these had effusion, requiring tapping; 3 out of the 8 cases of pleurisy occurred in those with tuberculosis in their family history.

Symptomatology. It is extremely difficult to draw any hard and fast lines as to whether the onset of the disease was acute or gradual; patients showing upon examination evident ascites or abdominal masses would date their beginning symptoms to abdominal pain of a few days' duration. In 66 cases it is stated as of gradual onset; in 29 as acute; in 3 it is not stated. Tightness of clothing may be the first thing noticed, or, as in 1 case, pregnancy may be thought present.

Abdominal Pain. This was noticed in 68 cases. One patient, not included in this series, as the operation occurred in 1900, had had abdominal pain for seventeen years, or since the age of eighteen. At operation the intestines and omentum were bound together by firmly organized adhesions extending into the pelvis, matting together the tubes and ovaries. On the parietal peritoneum several small calcified tubercles were found. The pathologic report of a small piece of the peritoneum over the cecum filled with minute grayish granulations showed the process to be tuberculous.

Diarrhea. In 23 cases diarrhea is recorded as present for a longer or shorter time.

Nausea and Vomiting. In 28 cases nausea or nausea and vomiting were present.

Fluid in Abdomen. In 63 cases there was fluid in the peritoneal cavity. In 26 cases the abdomen was tapped, either for relief or for diagnosis. The character of the fluid obtained either at tapping or at

operation was as follows: In 22 cases it was clear; in 6 it was bloody or slightly bloody; in 1 case it was high in color; in 5 cases pus was present; in 1 case it was chylous; in 4 it was greenish; in 2 it was brown; in 1 turbid. In 14 cases the specific gravity of the fluid is recorded. The highest was 1035; the lowest, 1008. In 10 of the 14 cases the specific gravity was above 1020. The highest percentage of albumin was 3.4 per cent.; the lowest, 0.1 per cent.

Masses. Masses are recorded as present in 29 cases. On the right side, 5; right hypochondrium, 2; right iliac region, 4; right epigastrium, 1. On the left side, 1; left hypochondrium, 1; left low down, 1; left iliac region, 1. At umbilicus, 1; right and left umbilicus, 1; below umbilicus, 2; right to umbilicus, 1. Above pubes, 1; between recti, 1; in psoas, 1; iliac region, 1; in 4 not stated.

Crepitation. In 1 case it is reported present after tapping. One record states doubtful crepitation; 1 friction over the surface of the liver.

The superficial abdominal veins were dilated notably in 2 cases, both in children.

Tuberculin Reaction. In 13 cases tuberculin was injected as an aid to diagnosis. In 8 cases the reaction was positive; in 3 negative, and in 1 not satisfactory. In 1 other case reported as negative the temperature was irregular when it was given, and the reaction was considered negative. The use of tuberculin in relatively so small a number of the cases is due to the fact that its earliest use in this series was in 1896; that it is used practically in only one of the medical services. Its use is also limited by the fact that it can only be employed in those cases, the four-hourly chart of which shows slight rise of temperature above the normal. The preparation used is a 1 per cent. solution of Koch's 10 per cent. tuberculin. The dose now given is from 7 to 10 minims. Reaction consists in a rise in temperature (it may reach 105) with constitutional disturbance, as chilliness, headache, pain in the back, or malaise. That a negative reaction may at times be of diagnostic value is well illustrated by the following cases:

One patient in whom the probable diagnosis of tuberculous peritonitis was made had two tuberculin injections without reaction. Operation showed no tuberculosis of the peritoneum. She died one month later of probable renal disease.

Another patient discharged relieved, with diagnosis of tuberculous peritonitis, did not react to tuberculin. She had a recurrence of symptoms later, and was operated upon at another hospital, and an adenocystoma of the ovary was found; she has since been well.

Leukocytosis. If we accept 10,000 white cells as within normal limits, where the blood counts were made at all hours of the twenty-four, and under the most varied conditions, there were 34 out of a total of 46 cases which were below this number, or, 70.8 per cent. which had no leukocytosis. Where the white count is above 10,000, pus may or may not be present; if present it may be sterile, or it may contain a variety of organisms. One case with a white count of 13,000 contained streptococci and bacilli. One with 14,000 white cells was sterile. One of 11,000 contained the colon bacillus. In 3 cases where the leukocyte count was above 10,000, pus tubes were also present at the operation. The blood was otherwise not remarkable beyond an occasional moderate secondary anemia.

Diazo. In 12 cases the diazo-reaction was present. The test is practically limited to the medical sides. It may be more or less constant, fleeting, or absent. It seems to be of but little practical significance in this series of cases. It has occurred in cases with high temperature and in cases with normal or subnormal temperature.

Temperature. There is nothing characteristic about the temperature charts in the series. In 48 cases the temperature, as a rule, was above 100. In the remaining cases the range of temperature was from normal to 100, or from subnormal to normal with slight variations. The temperature was usually higher in the evening, occasionally reaching 104, rarely 105.

Stay in Hospital. The longest stay of any patient in the hospital in this series was 347 days; the shortest two days. The average stay was 43.5 days.

In brief, in the 98 cases of tuberculous peritonitis over one-half occurred between the ages of fifteen and thirty years, and two-thirds of the patients were females. In about one-fifth there seemed to be a distinct tubercular family history, while one-twelfth had had previous pleurisy. In two-thirds of the cases the onset was gradual; in about two-thirds abdominal pain and ascites were present, while about one-quarter had diarrhea and one-quarter nausea or nausea and vomiting. In a little less than one-third of the cases abdominal masses were present. In 8 out of 13 cases the tuberculin reaction was positive, and in two-thirds of the cases there was no leukocytosis. The diazo-reaction seemed to be unimportant in this series, and the temperature to show nothing characteristic.

The cases have been divided into medical and surgical. Many of the cases entered on the medical side and were transferred to the surgical for operation; a few entered the surgical side and were transferred

to the medical. There were 46 cases which are included under medical; there were 52 cases under surgical.

MEDICAL CASES.—Condition at discharge.

Relieved or improved	16	Well	2
Much relieved	6	Dead	7
Not relieved	10		—
Against advice or ?	5		46

SURGICAL CASES.—Condition at discharge.

Relieved or improved	24	Well	4
Much relieved	14	Dead	6
Not relieved	1		—
Against advice or ?	3		52

Of the 46 medical cases the end-result is known in 25; of the 52 surgical cases the end-result is known in 32; out of 98 medical and surgical cases the end-result is known in 57 cases, or 58.1 per cent.

The prognosis in a sense may be said to depend on the diagnosis. That there is liability of error in the diagnosis of tuberculous peritonitis may be inferred from the fact that the following cases have been considered as cases of tuberculosis of the peritoneum—the mistake has been shown at operation or at autopsy: Tuberculosis of retroperitoneal glands and pericardium; fibroma of ovary; lymphosarcoma of mesenteric glands and intestines, with perforation and general peritonitis; scirrhus cancer of the stomach with cancerous peritonitis; retention cysts with chronic peritonitis; colloid carcinoma; adenocystoma of ovary. Several of the cases, especially in the earlier part of the series, entering with high temperature, abdominal distention, absence of leukocytosis, with diazo, were at first considered to be cases of typhoid.

The prognosis as to life, if estimated from the hospital mortality, would be good in about 87 per cent. of the cases in this series. Seven cases died in the hospital out of 46 treated on the medical side, and 6 died out of the 52 treated on the surgical side; 13 in all out of 98 cases, a mortality of 13.2 per cent. A more accurate prognosis as to life can be formed by estimating the mortality from the whole number of cases in which the end-result is known. In 57 of the whole number of 98 cases the end-result has been obtained, covering a period of from two to eleven years after discharge from the hospital. The list follows:

Medical. Of the 16 cases discharged relieved or improved from the medical side, 9 have been heard from, 4 have died, 2 are well, and 3 have had no return of symptoms. Of 6 discharged much relieved, 2 have been heard from; both have died. Of 10 discharged not relieved, 6 have been heard from, 4 have died, 2 are well. Of 5 discharged

against advice or ? none have replied. One well at discharge had a recurrence, but is now well. Of 46 medical cases, including those who were discharged dead and those who have died outside, there have been 17 deaths, or 36.9 per cent. Of 25 medical cases in which the end-result is known, 17 have died, or 68 per cent.

1. Uncomplicated	Died at home in a few months.
2. Tuberculous peritonitis and phthisis .	Discharged dead.
3. Uncomplicated	Died at home; brain fever six months.
4. Tuberculous peritonitis and pleurisy .	Discharged dead.
5. Tuberculous peritonitis (pleurisy one year before).	Died outside in one month.
6. Uncomplicated	Died in three and a half years of phthisis.
7. Tuberculous peritonitis and nephritis?.	Discharged dead.
8. Tuberculous peritonitis, phthisis, and nephritis.	Died at home in a few weeks.
9. Uncomplicated	Dead four months; general tuberculosis and cirrhosis of liver.
10. Uncomplicated	Died four years. Cause?
11. Uncomplicated	Discharged dead.
12. Tuberculous peritonitis and tuberculous pleurisy.	Discharged dead. Autopsy: Chronic tuberculosis of pleura and peritoneum.
13. Tuberculous peritonitis, cardiorenal .	Discharged dead. Autopsy: Tuberculous peritonitis, tuberculous liver, chronic nephritis, and hypertrophied heart.
14. Tuberculous peritonitis, glandular .	Dead four years.
15. Tuberculous peritonitis, phthisis (?), and fistula.	Dead a few months.
16. Tuberculous peritonitis and phthisis .	Dead four months.
17. Tuberculous peritonitis, fistula from tapping, and rachitis.	Discharged dead. Autopsy: Tuberculous peritonitis, focal tuberculous liver, spleen and kidneys; tuberculous mediastinal and postmesenteric glands; no ulcers in intestines; puncture wound of abdomen.

The high mortality of 68 per cent. of those patients having received only medical treatment may in part be accounted for by the fact that in only 6 of these cases was the tuberculous peritonitis uncomplicated, as shown by physical examination during their stay in the hospital. The other 11 cases showed one or more of the following complications: Phthisis, fistula, tuberculous glands, rickets, pleurisy, cardiac or renal disease. Three cases in which postmortem examinations were obtained also showed evidence of tuberculous infection elsewhere.

Surgical. Of 24 cases discharged relieved or improved, 11 have been heard from—3 are dead, 1 has had a recurrence and is now better, 7 are well. Of 14 cases discharged much relieved, 10 have been heard from—2 are dead, 1 is better, and 7 are well; 1 case discharged not relieved, died within one month. Of 3 cases discharged against advice or ?, 1 replied and was well two years later. Of 4 cases discharged well, 3 have reported well. Of 52 cases surgical, including

those discharged dead and those who died outside, there have been 12 deaths, or 23 per cent.

1. Discharged dead, ten weeks after operation; pus and fecal fistula.
2. Discharged dead. Sinus persisted, and died twenty-four hours after second operation.
3. Discharged dead, twenty-four hours after operation. Autopsy: Tuberculous peritonitis, local peritonitis, healed focus in lung.
4. Discharged dead, twelve hours after operation.
5. Discharged dead, eleven days after operation; peritonitis and fecal fistula.
6. Discharged dead, seven weeks after operation; early autopsy record not to be found.
7. Discharged, relieved or improved. Dead three months; general sloughing of wound (gall-bladder).
8. Discharged, relieved or improved. Dead two months; fluid returned, tapped.
9. Discharged, relieved or improved. Dead four years; tuberculosis of pleura and peritoneum.
10. Discharged, much relieved. Dead four months; "bowels decayed."
11. Discharged, much relieved. Dead nine months; phthisis.
12. Discharged, not relieved. Dead one month (?); (gall-bladder).

The prognosis as to life when viewed from the end-result obtained in 57 cases of this same series gives a mortality of 47.3 per cent. (2 cases in which the cause of death is doubtful have been excluded), instead of the hospital mortality of 13.2 per cent.

It is interesting to note that of the 16 cases which have died since leaving the hospital, 10 died within a few weeks or months of the time of discharge. Four years was the longest period that any of these patients lived after discharge.

Prognosis as to Recovery. Of the 8 cases heard from treated medically in which there has been no return or which are now well, the length of time intervening is as follows:

1 well 11 years
1 recurrence 1 year later, now well 7 years . . or 1 patient 11 years.
1 no returns 5 years . . . . . " 1 " 7 "
1 good health 5 years . . . . . " 2 patients 5 "
1 well 3 years . . . . . " 2 " 3 "
1 good health 3 years . . . . . " 2 " 2 "
1 no return 2 years 3 months.
1 no return 2 years.

Of 32 surgical cases in which the end-result is known up to the present time, 20 are better, or have had recurrence and are now well.

4 cases	2 to 3 years.	4 cases . . .	6 to 7 years.
3 "	3 " 4 "	2 " . . .	7 " 8 "
2 "	4 " 5 "	3 " . . .	8 " 9 "
1 case	5 " 6 "	1 case . . .	9 " 10 "

Of 25 cases treated on the medical side, 68 per cent. have died, 32 per cent. are now well or have had no return of symptoms or have had a recurrence and are now well (1 case).

Of 32 surgical cases in which the end-result is known, 37.5 per cent. have died, 62.5 per cent. are better, well, or have had a recurrence and are now well.

Recurrence. In 2 patients recurrence has occurred, but both are now well.

Character of Fluid, with a View to Prognosis. In 4 cases in this series in which pus was present, 1 died of fecal fistula, 1 had a fecal fistula and recovered two and one-half years; 1 a persistent sinus, now better two years; 1 local sepsis, well two years. In 4 cases which have been heard from in which the fluid was bloody or slightly bloody, 1 died in a few months; 2 well six years; 1 well nine years. One case heard from in whom the fluid was turbid has been well two years. In 14 cases heard from in which the fluid was clear, 9 are dead; 4 are well; 1 is better.

Absence of Fluid. In 7 cases heard from without fluid, 1 has died, 6 are well.

Masses. In 19 cases with masses heard from, 12 have died, 7 have recovered, or a mortality of 37 per cent. In 30 cases with ascites without masses, 12 have recovered, 18 have died, or a mortality of 60 per cent.

Treatment. The treatment on the medical side was in the main symptomatic and hygienic. Tapping was resorted to whenever necessary for the comfort of the patient. The treatment on the surgical side consisted of simple abdominal incision, sponging or washing out of the abdominal cavity with normal salt solution or sterile water, and removal of masses of tuberculous material when possible. In 8 cases one or both tubes were removed at the time of operation; 32 of these cases were sewed up tight, 20 were drained with gauze or tubing. The pathologic report is stated as tuberculous in 26.

Of those cases with ascites treated medically and tapped, the record is complete in 10; 7 were discharged dead or have died since discharge, 1 is well after an interval of eleven years, 1 has no return at five years, 1 no return in two years and three months.

Of especial interest of those cases which were tapped are the following: A woman, aged fifty years, entered the Massachusetts General Hospital in 1894 with tuberculosis of the peritoneum and glandular tuberculosis. There was marked ascites. She was tapped and discharged relieved. She re-entered one year and six months later, saying her health had been excellent since leaving the hospital. She had, however, lost flesh and color. Two months after leaving the hospital her abdomen was again tapped and nine quarts of serum withdrawn. In the preceding eight months before her re-entrance the abdominal swelling had increased so that she had to give up work. At re-entrance her abdomen was very much distended and fourteen and three-quarter

quarts of fluid was withdrawn. Specific gravity, 1022; albumin, 3.4 per cent. She was discharged relieved, but died in 1898, four years after her first entrance.

A farmer, aged nineteen years, single, entered the hospital in September, 1889. One year previous glands of neck had suppurated, one abscess opened (a few months after recovery from mumps). With this there was some bronchial trouble, from which he recovered. Two weeks before entrance he took cold, had a headache, backache, soreness in lower part of the abdomen. At entrance there was some ascites, which disappeared after one week. Three weeks after entrance one of the glands of the neck opened. He was transferred to the medical side, and three days after transfer the record states: "Encysted fluid in abdomen, some fluid in right pleural cavity, questionable right apex." He was kept out-of-doors daily, and January 4, 1890, the gland had nearly stopped discharging, the fluid had disappeared from the chest, there was still a little ascites. He was discharged on the above date, having shown steady improvement. He re-entered November 3, 1890. Except for a touch of "la grippe," had been improving. The abdomen had remained about the same, there was slight suppuration from one gland of the neck. Other scars had closed. There was some ascites present, and he was tapped November 8, 1890. Three and one-half quarts of slightly bloody fluid, with specific gravity 1017, and with much albumin, was removed. He was discharged November 20th, doing well. He reported December 20, 1890, looking much better. There was some resistance in the right flank. On March 8, 1891, "Feels as well as ever." Reported October 14, 1891, said that he had caries of rib, which had been tapped, drained, and later curetted. This was now nearly healed. Weight, 134¾ pounds. Had been doing light work on a farm and had never felt better in his life. October 19, 1892, "Never better, no symptoms, no cough," weight 140 pounds. May 16, 1896, rides a bicycle ten to twenty miles a day, no cough, feels well. November, 1901, reported excellent health.

Of those cases treated medically in which there were abdominal masses the record is complete in 6; 3 have died, 1 had no return, and 2 are in good health. Of this number the following case is of interest:

A woman, aged twenty-six years, with abdominal pain of eight months' duration, with masses in the right hypochondrium, who gave a reaction to tuberculin, was discharged unrelieved after a two weeks' stay in the hospital. She was told of her condition and advised to live out-of-doors as much as possible. She went immediately to the seashore, where she says she had plenty of fresh air and good food.

She rested for one entire year. Since that time she has been working constantly and considers her condition to be excellent. It is at present six years since discharge.

It has seemed well to record the ill results of operation. Fecal fistula occurred 6 times; 2 died in hospital; 1 recovered; 3 not heard from since discharge.

Local Abscess. Three cases: 1 died in hospital after second operation; 2 not heard from.

Shock of Operation. Two patients died within twenty-four hours.

Local Sepsis. Two cases: 1 died in three months; 1 recovered. In 2 cases sinuses persisted, ultimate recovery two years and four months, respectively. One case died four months, "decayed bowels." Two died, return of disease, four years and two months, respectively. There was 1 case of phlebitis and 1 case of hernia in the scar of operation. In 2 cases on the medical side the intestines were punctured during tapping; 1 with no ill result; 1 with development of fecal fistula.

CONCLUSIONS. The mortality when based on the condition of the patients at discharge, in a series of 98 cases of tuberculous peritonitis at the Massachusetts General Hospital, is 13.2 per cent. The mortality of the same series of cases after a period of from two to eleven years is, on the contrary, 47.3 per cent. The ultimate mortality of patients n this series under medical treatment is 68 per cent.; under surgical treatment 37.5 per cent.; 2 patients have had recurrence, but are now well. None of the other patients at present report themselves as suffering from the disease.

In conclusion, I must confess that I am somewhat disappointed by not getting as definite indications from this series of cases as I had hoped for.

Recognizing that the number of cases is not large, and that in many of those reporting themselves as now well the lapse of time is, after all, relatively short, I am disposed to state the main therapeutic lessons which I derive from the analysis as follows:

1. Tuberculous peritonitis may be followed by apparently complete recovery, even if complicated by tuberculosis elsewhere either under (*a*) purely medical treatment; (*b*) tapping; (*c*) incision.

2. As in other forms of internal tuberculosis, the best obtainable hygienic surroundings are all important. Consequently no patient should be kept in the hospital longer than is necessary, especially if more and better air can be secured outside with proper care and food.

3. We are warranted in trying medical treatment for a time, especially under first-rate hygienic conditions, tapping the abdomen if there is sufficient fluid to cause discomfort.

4. If the patient under a month or six weeks of medical treatment fails to improve, or in even less time if he seems to be losing ground, surgical treatment should be advised.

DISCUSSION.

DR. TYSON: I should like to refer to a case of tuberculous peritonitis that came under my care about fifteen months ago. A young girl, between fourteen and fifteen years of age, had ascites without any further evidence of the disease whatever; no evidence of tuberculosis of the lungs, no fever, and nothing except this effusion. She was advised to enter the hospital of the University of Pennsylvania, where the tuberculin test was made. The response was positive, and Dr. John G. Clark operated, opening and draining the abdominal cavity. Within the month she left the hospital perfectly well, and has remained so for fifteen months. The operation confirmed also the diagnosis of tuberculous peritonitis. My own feeling is that it is hardly worth while to temporize with medical treatment in these cases, as the result of surgical treatment is so satisfactory, while in my hands the medical treatment has been practically worthless.

I should like to refer to another case of tuberculous peritonitis with ascites, in the diagnosis of which I was misled because it was associated with an enlarged liver and was looked upon as a case of interstitial hepatitis with effusion. Autopsy revealed typical tuberculous peritonitis. I feel confident that the tuberculin test should be tried in every case of apparent cirrhosis of the liver with ascites, and believe that more of them than we might expect will turn out to be cases of tuberculosis of the peritoneum.

DR. BRANNAN: On seeing the title of this paper upon our program I looked over the records of Bellevue Hospital for the last ten years, and I have only found eighteen cases with records sufficiently complete to warrant reporting. In so far as they go they agree with Dr. Shattuck's conclusions, and the surgical treatment gave better results than medical treatment. Ten cases were treated medicinally in the manner outlined by Dr. Shattuck, and of these six died, one recovered, one improved, and two left unimproved. Laparotomy was performed in six cases, with only one death. All the others improved. In two cases of the eighteen in which the diagnosis was doubtful, one was a medical case that recovered and the other the surgical case that died. The surgical case was probably one of appendicitis with general peritonitis following.

DR. DANFORTH: I should like to refer to a case from my own experience, which was apparently a case of tuberculous peritonitis. It remained under my care for something like two months, and I had two surgeons of large experience in consultation. We all agreed that drainage was necessary, and

the time for operation was fixed. Meantime a faith-curer came along, and we three physicians were incontinently discharged. The girl was about eighteen years of age, and she recovered in about six months after my dismissal, without any treatment at all, and she remains well still, after a lapse of five years. It appeared to those of us who were concerned in the case that we must have been mistaken in our diagnosis. The tuberculin test was not tried, but I am still wondering how the signs and symptoms managed to counterfeit tuberculous peritonitis so perfectly.

DR. BILLINGS: It seems to me that we should consider the morbid anatomy of tuberculosis of the peritoneum when deciding upon medical or surgical treatment, respectively. Clinically, the cases may be divided into three groups: First, those in which there is a serofibrinous exudate, with perhaps a focus in a Fallopian tube, or in the bowel or elsewhere, with miliary tubercles scattered over the peritoneal surface. Second, those cases with a seropurulent exudate, with or without blood, and with infiltration of the mesenteric glands, peritoneum, omentum, and mesentery, and associated with the usual shrinkage and distortion of these parts. Large tuberculous granulomata are frequently present with adhesions between the peritoneal surfaces, and the peritoneum is frequently swollen, red, very fragile, and easily torn. Third, those cases in which there is little or no exudate, the chief morbid anatomic condition being one of adhesions between coils of intestine and between the intestine and the abdominal wall, which partially or completely obliterate the peritoneal cavity.

In the first class of cases recovery frequently occurs spontaneously, and surgical interference appears to be helpful. In the second class of cases surgery can do but little, and the great majority of patients die, it matters not what treatment is used. In the third class of cases operation is out of the question, and when an operation is performed more harm than good is usually done.

At the Presbyterian Hospital I have been treating the cases with serofibrinous exudate with the X-ray and rest in bed, and I have been very much gratified with the improvement which has taken place.

The late Dr. Fenger, who was a surgeon with all that word implies, and not a mere operator, wrote just before his death a classical article on the subject of tuberculous peritonitis. He practically condemned operative interference in the disease.

DR. MELTZER: I should like to record a case of tuberculous peritonitis apparently cured by a laparotomy, which is just now under my observation. About a year ago I had a young girl of eighteen years under my care who presented mild symptoms of appendicitis. She had moderate pains in the ileocecal region, slight muscular rigidity of the right side of the abdomen, and moderate tympanites. She had a pulse of 80, and the temperature varied between 99.4° and 99.8°. I had her under observation only four days, when I decided to have her operated on, for the following reasons: Just a year

before the same patient had pleurisy with serous effusion, which had to be evacuated twice. There were at that time neither physical nor bacteriologic signs of tuberculosis; neither is there any tuberculosis in the family history. The pleurisy was followed by distinct articular rheumatism, which yielded to treatment with sodium salicylate. During the year intervening between her pleurisy and the present attack of apparent appendicitis the patient was perfectly well, and certainly showed no symptoms indicating tuberculosis. Nevertheless, I could not suppress my suspicion that the symptoms of appendicitis might be due to tuberculosis of the peritoneum. Dr. McBurney, whom I consulted, could not find any symptoms to substantiate my suspicion, but agreed with me that the patient should be operated on. At the operation four quarts of yellow serous fluid was evacuated, and the serous covering of the appendix as well as of the accessible parts of the intestines were studded with tubercles. The appendix was removed and the wound was kept open by means of a glass drainage tube for over two weeks. It is now about a year since the operation. For nine months I had the temperature of this patient taken twice a day, and it was never above 99° except for a day previous to her menstruations. She is to all appearances perfectly cured of her tuberculous peritonitis; but I am fully aware that we cannot pronounce such a case as really cured unless five years at least have passed after the operation. I have to confess that for eleven months I gave this patient three times a day theocol, a creasote compound prepared by Merck. Two points I would like to bring out with regard to this case. In the first place, it is the fact that there were no physical symptoms for a diagnosis of tuberculous peritonitis, and it was only the preceding attack of pleurisy which prompted me to have her operated on, for the mild symptoms of appendicitis alone I would not have thought of an operation. The second point is rather a surgical one. It would seem to me that in all cases of tuberculous peritonitis an intramuscular incision, as it is done in operations for chronic appendicitis, should be preferable to one in the linea alba. It would prevent the occurrence of a hernia, which is the more liable to happen in such cases of tuberculous peritonitis which are complicated by pulmonary coughs.

THE PRESIDENT: I had intended calling on Dr. Halsted, since no one is better able to advise on surgical matters, and I am sure the Association will be pleased to hear from him.

DR. HALSTED: Our experience has not been very large in this line of work, but it has, on the whole, been very satisfactory, and our results conform closely to those mentioned by Dr. Shattuck. We have benefited very much, I am sure, some cases which were much more advanced than those to which Dr. Billings referred; that is, we have improved some that had decidedly large tuberculous masses, and also tuberculous glands, which clearly could not have been removed. I am glad to say that I can endorse what Dr. Trudeau has said with regard to the diagnostic use of tuberculin. We

have been using it systematically for eight years, and we have yet to record a case proven to be tuberculous in which tuberculin failed. Dr. Shattuck mentioned a number of cases in which it had apparently failed, and I can understand how that might be. For instance, unless these injections are watched very carefully by someone interested in them, it may happen that the case would not give the reaction at the first dose. We have had a number of cases in which the solid metal syringe was used and no reaction followed for perhaps nine minutes, but when a glass syringe was used and the injection controlled we have never failed. I should emphasize the fact that if one does not obtain a reaction in a given case the reason therefor should be carefully sought.

DR. VAUGHAN: At least one important piece of knowledge has been obtained through operative treatment of tuberculous peritonitis. By means of this operation we have seen that tuberculous lesions may completely heal, and that there may be a complete *restitutio ad integrum*. A few years ago I inoculated a number of rabbits intra-abdominally with pure cultures of the tubercle bacillus. After periods ranging from four to eight weeks I made abdominal section of a number of these animals, and made notes of the lesions observed at that time. In all instances the great omentum was tuberculous, and in many the peritoneum and the liver contained small tuberculous nodules. After noting the condition in each animal I sewed up the abdominal wound and left the animals to themselves for periods varying from three to nine months. A number of them apparently recovered, and when a second abdominal section was made it was found that in some the tuberculous lesions had wholly disappeared.

DR. JACOBI: I can only give my impressions from having seen a large number of cases, the most of which occurred in children, and I shall speak particularly of them. It is a fact in children that so long as tuberculosis is not disseminated we may expect recovery to take place. When, however, it becomes disseminated there is very little hope for either medical or surgical treatment. I have seen so many cases get well without operation that I have no doubt that too many laparotomies are performed. I see these cases getting well without any treatment at all, and under various forms of treatment, but I have never seen one get well when the tuberculosis was disseminated. It is possible, however, that we shall have to revise this whole chapter of the nature of tuberculosis after what we have heard at this meeting from Dr. Abbott.

DR. SHATTUCK: I wish I could quite share the views which Dr. Billings has expressed, as they would be very helpful if true. I do not mean that they are not true, only that I am not convinced. And they are at variance with our experience at the Massachusetts General Hospital, as is clearly shown by a paragraph which I omitted from the abstract of the paper as read.

Of nineteen cases with masses treated surgically and heard from, twelve have died, a mortality of 37 per cent. Of thirty cases with ascites and without masses treated surgically and heard from, eighteen have died, a mortality of 60 per cent.

Just a word with regard to Dr. Jacobi's opinion that much depends on the extent of the tuberculous process. I suppose this is true beyond a doubt; and yet it is not absolutely true. The longest case in my series dates back eleven years, and has been perfectly well for eight years. And yet he had simultaneously or successively signs of tuberculosis of the lung, pleura, peritoneum, glands, and bone. I drew off a quart of encapsulated serous fluid from his peritoneum, tapping at McBurney's point.

PROGNOSIS OF PLEURISY WITH SEROUS EFFUSION.

By RICHARD C. CABOT, M.D.,
of Boston.

I have undertaken in this paper to study the outcome of cases of pleurisy in which there was good evidence for believing that a serous effusion was present, but in which there was no evidence of tuberculosis either in the lung or in other organs. I have excluded all cases in which the signs pointed only to a dry pleurisy or to a chronic pleural thickening, as well as those in which the effusion was known to be purulent, also all in which there was evidence of tuberculosis in the lung or in any other organ. In the group of cases so defined I have studied the following problems:

1. What are the chances that a patient who has had pleural effusion will later become more tuberculous than the rest of us—that is, will show a degree of tuberculosis demonstrable by our present methods of examination? I assume in this that we have all of us our bit of tuberculosis, and that the important question is how much we have.

2. In case the patient does become "tuberculous" in the sense above defined, what is the severity and what the rate of progress in the average case?

3. In case the patient does not manifest any signs of tuberculosis after recovery from the pleurisy, is he likely to develop any other disease which can reasonably be supposed to be due to the pleurisy?

4. Is there anything in the physical signs or in the history of cases of pleural effusion which should enable us to predict what will be the ultimate outcome of the case, whether recovery will be complete and permanent?

5. How long a time must elapse after the occurrence of the pleural effusion before the patient can consider himself free from the danger of contracting tuberculosis?

In studying these problems my material has consisted of 154 cases of pleural effusion, which I have followed up by the letter and by personal visit after their apparent recovery. The total number sought for was 300.

An analysis of these cases shows the following statistics:

GROUP I.

Number living and sound after 15 to 20 years or more	21
Number living and sound after 10 to 15 years or more	23
Number living and sound after 5 to 10 years or more	36
Total over 5 years	80

GROUP II.

Number living and sound 4 years after	14
Number living and sound 3 years after	7
Number living and sound 2 years after	16
Total under 5 years	37

GROUP III.

Number died of other trouble not tuberculous and not obviously connected with the pleurisy:

After 10 years or more	1
After 5 years or more	2
After 2 to 5 years or more	11
Total	14

GROUP IV.

Number contracted tuberculosis 16 years later	1
Number contracted tuberculosis 10 to 15 years later	4
Number contracted tuberculosis 5 to 10 years later	8
Number contracted tuberculosis 1 to 5 years later	10
Total	23

Six of this last group still live.

Groups I., III., and IV. make up 117 cases, which were followed for at least five years or until death. Ninety-four of these, or 80 per cent., were apparently well at the end of five years.

On the basis of the above statistics I am led to the following conclusions:

1. Eighty per cent. of the cases of uncomplicated serous pleurisy are in good health after five years or more (more than half of these have been followed for ten years or more).

2. Ninety per cent. are apparently in full health at the end of from two to five years—that is, the pleurisy had no *immediate* connection with any other affection.

3. Fifteen per cent. of the cases have sooner or later developed demonstrable tuberculosis of lung or bone, but in only 3 per cent. has this tuberculosis manifested itself within two years of the date of pleural effusion.

4. The type of tuberculosis which occurred in these cases was, as a rule, mild and of slow course. Death did not occur until five years or more after the pleurisy in one-half of the 23 cases which developed obvious tuberculosis. Six of the 23 are still alive, despite the tuberculosis, after periods of ten, nine, six, four, two, and one year.

5. Nevertheless, a very rapid form of tuberculosis may develop many years after the pleurisy—nine years and sixteen years, respectively, in two cases of this series—so that the patient is never safe from the possibility of death from tuberculosis merely because his pleurisy lies ten or fifteen years behind him.

6. A study of the clinical records of the whole group of patients under consideration shows that among those who have remained in perfect health for five years or more only 25 per cent. had any family history or past history of tuberculosis, while of those who have become tuberculous 67 per cent. had tuberculosis in their immediate family or in their own past history. A careful history, therefore, is of great importance in the prognosis of pleural effusion.

On the other hand, the physical signs during the course and convalescence of the pleurisy were not markedly different in the group of cases in which tuberculosis later developed from the signs in those who have remained well.

7. Recurrence of the pleurisy itself in patients who have recovered from the original attack occurred in only five cases, or 3 per cent. of this series.

Reaccumulation of the fluid immediately after tapping is rare, occurring in only two cases, or $1\frac{3}{10}$ per cent.

8. Among the 14 patients who after recovering from the pleurisy died of some other disease not one developed any disease which could

reasonably be considered a result of the pleurisy (the causes of death were alcoholism, hepatic cancer, dysentery, pulmonary embolism, mitral stenosis, aortic regurgitation, chronic nephritis (3), cerebral hemorrhage, measles, pneumonia (3).

9. Finally, I could call attention to the fact that I have made no attempt to discover what percentage of this whole group of cases is due to tuberculosis. So far as my statistics go the cases may be all of tuberculous origin.

What my figures do tend to prove is that whether pleurisy means tuberculosis or not, the outlook is bright provided no family history of tuberculosis clouds it. If pleurisy means tuberculosis, it is a very mild form of tuberculosis, and one from which recovery is usually complete under proper treatment. Even if pulmonary tuberculosis later makes itself manifest the type of disease is unusually mild.

It might be objected that I have been able to trace only the more favorable cases, the others being lost sight of. But a glance at the table shows that it contains 27 deaths, and, in fact, these were the cases in which information was most easily and promptly secured. It was the patients who have completely recovered which I found it most difficult to trace.

The man who becomes consumptive and dies is a marked and interesting figure to his tenement neighbors, and his case is well remembered. But the ordinary healthy neighbor makes comparatively little impression, and his migrations are proportionally difficult to trace.

DISCUSSION.

DR. OSLER: I do not think such an important paper should pass without some comment, at any rate not without an acknowledgment of our debt of gratitude to Dr. Cabot for his work in going over such a large series of cases. It will be refreshing to take these figures home with us, since we have of late years felt that a patient with a serous effusion surely had tuberculosis. These figures are much more favorable than those given in Dr. Bowditch's table, which, if I remember rightly, gives a percentage of 33 per cent. dying subsequently of tuberculosis.

DR. HARRIS: This paper is of great interest, because we have had the impression, just as Dr. Osler has said, that the prognosis as regards a serous pleurisy was much graver than these figures would lead one to suppose.

Certainly our practice in England is based upon figures much more unfavorable than these. In England pleurisy is certainly regarded very seriously by the life insurance companies, and it is the rule now not to accept any applicant who has had pleurisy within a period of five years. It is also the custom to regard any case of pleurisy occurring in young subjects as of tuberculous origin, and that a large proportion of those subjects will within five years become claims upon the societies as the result of tuberculosis. These figures will make us think twice as to whether these rules were not too strict upon the people, and too much, as all laws are, in favor of all the insurance companies.

DR. JACOBI: There is one more fact which proves that these figures are more nearly correct than those usually given, and that is, that no matter what a patient complains of, you frequently find, when you come to examine him, the remnants of an old pleurisy; there is over the whole side of the chest a dulness that can be explained by nothing else but a previous pleurisy. Such a condition is very common, and proves exactly that the prognosis in serous pleurisy should not be so very unfavorable.

DR. VAUGHAN: I am very much gratified at the conclusions drawn, but I do not see that one of them is altogether justified. Some fifteen or twenty years ago Fleming laid down the law that pleurisy always meant tuberculosis, and if limited to one side it meant tuberculosis of the apex on the other side. We know that is not true; but it seems to me Dr. Cabot's figures here give us too rosy a view of the matter. Now, as I understand it, some of these cases date back twenty-one years, and of the 300 cases recorded Dr. Cabot was able to find only 152. Is it not to be presumed that of the 148 others most of them are dead? What did they die of?

DR. CABOT: One word in confirmation of what Dr. Jacobi has said. I did not think the evidence sufficiently clear to include it in the paper, but I went through the records of 1000 autopsies, and I found that in 25 per cent. there had been a pleurisy on one side without any record on the clinical charts to suggest it. It suggests that our prognosis need not be as bad as has been supposed heretofore.

In answer to Dr. Vaughan, I would say that a considerable proportion of the cases I was able to trace up had died, and that I did not get hold simply of the cases that lived. In the second place, these 152 cases were pretty evenly distributed over two decades. Further, I have found that it is those who are still alive and well who are hardest to trace. The sick man makes a lasting impression on his neighbors' minds, and his death is long remembered. The wanderings of the sound neighbor are less noticed.

REPORT OF THE PRESENCE OF ANGUILLULA ACETI IN THE URINE OF TWO PATIENTS, MISTAKEN FOR STRONGYLOIDES INTESTINALIS.

By FRANK BILLINGS, M.D., and JOSEPH L. MILLER, M.D.,
of Chicago.

About three years ago we had an opportunity to examine a specimen of urine sent to Dr. Billings, where the diagnosis of filariasis had been made, based on the presence of a nematode in the urine which resembled somewhat the filaria sanguinis hominis. The physician in attendance reported that the patient had suffered for a considerable time with symptoms pointing to irritation of the urinary tract, hematuria, and frequent micturition. Other symptoms were slight edema of the legs and moderate drowsiness. The physician noticed, macroscopically, in the specimens of urine which the patient brought with him, a number of small, very actively motile worms, which on microscopic examination he considered filaria; otherwise nothing pathologic was detected in the urine. It was alkaline in reaction, free from albumin and sugar, and was not chylous. Although repeated subsequent examinations were made, they were all negative, as the worms were only found in the one specimen.

The blood of the patient was carefully examined for filaria, with negative results.

At the time the urine was received only a cursory examination was made, and a few permanent microscopic slides were prepared for future reference. An examination of these a few weeks later convinced us that the nematode present was not the filaria. A few of the smaller worms present were only slightly longer than the filaria. Many were found, however, 1 mm. in length, which is two or three times the length of the filaria embryos. The characteristic sheath of the filaria was absent. The mouth, shape of the head, and gradually tapering posterior extremity did not correspond with these parts in

the filaria. They conformed, however, both in size and structure with another parasitic worm—the Anguillula stercoralis or intestinalis. The peculiar pharynx, esophagus, and stomach, and the characteristic hooks of the male, stamped it as a member at least of this family.

A few weeks later we had an opportunity to examine microscopically the urine from a second patient, a lady, in which a similar nematode was found, and where the probable diagnosis of filariasis had been made. In this case also the urine had been collected in a bottle previous to the examination.

Normand first discovered the Anguillula stercoralis in the stools of patients who had contracted diarrhea in Cochin China. Since then they have been associated with diarrhea in various parts of the world, in Switzerland, Germany, Russia, Manila, and Brazil. Strong recently reported the first case in North America, and Thayer (*Journ. of Exper. Med.*, Nov. 29, 1901) reports two cases, one of which at least must have originated in this country. The other patient was an Austrian who had lived in America six years.

This nematode is referred to in the literature under various synonymous terms as Anguillula intestinalis, Strongyloides intestinalis, Rhabditis stercoralis, Leptodera stercoralis, Leptodera intestinalis, Rhabdonoma strongyloides, and Rhabdonoma intestinalis. Those wishing a full description with literature should consult Dr. Strong's article (*Johns Hopkins Hospital Reports*, vol. x.), or the article by Dr. Thayer, previously referred to. In the following description only a few of the more essential points will be considered.

The Anguillula stercoralis and the Anguillula intestinalis were described as distinct species until Leuchart, in 1882, demonstrated that the former was the free form, the latter the parasitic form, of the same species. Its etiologic relation to the diarrhea has not yet been fully established, although from the researches of Strong and others their ability to cause pathologic changes in the mucous membrane of the intestine must be admitted. The free forms are found in the stools; the parasitic forms and ova in the intestines, the parasites being sometimes found in the crypts of Lieberkühn, where they cause atrophy of the epithelial cells and often slight round-cell infiltration. The two forms can better be described separately, on account of their differences in size.

The free forms found in the feces are 0.3 to 0.6 mm. in length, 0.016 to 0.022 mm. wide. Placed in the incubator they moult, increasing in size, the mature males reaching 0.75 to 1 mm. in length by 0.04 to 0.06 mm. in breadth; the females, 1 to 1.4 mm. by 0.075 mm. The head is rounded, the mouth surrounded by four papillæ. The esophagus presents two enlargements connected by a narrow constricted portion. The second enlargement is top-shaped and contains three chitinous teeth arranged like the letter "Y." Continuous with this second enlargement or stomach are the intestines, which terminate at the anal opening near the posterior extremity. The males have a pair of double-curved hooks in the anal region used in copulation. The female sexual orifice is at the junction of the posterior with the middle third of the body. Elipsoid ova, 0.17 mm. by 0.045 mm., and also at times free embryos, can be seen in the uterus.

The females of the parasitic forms are much larger, and present slight structural differences from the above. Length, 2 to 2.25 mm.; width, 0.0132 to 0.04 mm. The mouth is without papillæ, and the esophagus is one-fourth the length of the entire body and without enlargements. The ova measure 0.06 by 0.034 mm.

In the permanent preparations made from the urine only the male forms were found. These varied greatly in size, the smallest found 0.3 mm., the largest 1.2 mm. in length by 0.03 mm. in diameter. The form resembled very closely the drawings of Anguillula stercoralis found in the various works consulted. The terminal mouth was succeeded by an oblong pharynx, a narrow esophagus connecting it with a top-shaped stomach. The characteristic curved spicules were present in the mature males. The tail tapered gradually to a very fine point. The anal opening, a curved cleft, was located near the posterior extremity on the ventral surface. The intestinal canal was surrounded by a layer of cells containing numerous fat particles.

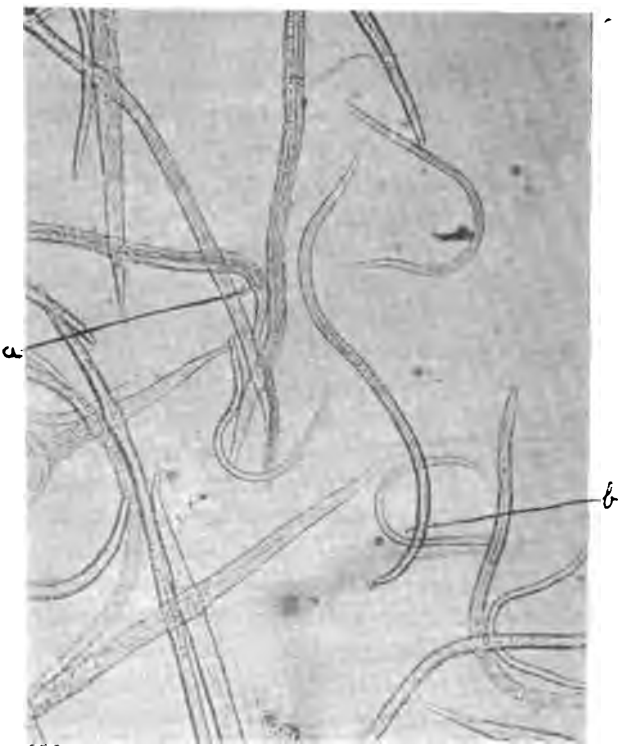
With the above findings the identification of the worms was apparently established, but several interesting features in these two cases lead to a further study.

1. Throughout the literature no report could be found where the Anguillula stercoralis had been present in the urine. Sheiber (*Virchow's Archiv*, 1880) reported finding a nematode belonging to this genus in the urine of a woman. From his description it is impossible

to determine whether the worm was the Anguillula stercoralis or a related species. In Sheiber's case they were found repeatedly until a careful cleansing of the genitalia demonstrated that the worms were not passed in the urine from the bladder.

2. They were found only once in the urine of each of these patients, although in one case, at least, repeated examinations were made.

FIG. 1.



Vinegar eel. *a*. Protruded hook of male showing fan-shaped accessory piece. *b*. Top-shaped esophageal enlargement. Magnified 60 times.

3. They were both times found in urine that had previously been collected in a bottle, thus allowing of contamination. Furthermore, the presence of these two cases in an interval of a few weeks was also remarkable. With these points in mind, a further study was made of this family.

The family anguillulidæ is represented by numerous genera scattered over the entire world. They are found in fresh and salt water, in the mud of ponds, in decaying vegetable matter, etc. A number are parasites having as a host the lower forms of fresh and salt water animal life. Bastian (*Trans. Linn. Soc.*, vol. xxv.) describes and gives drawings of one hundred new species which he discovered. He also enumerates a large number of species previously described by others. Borellus, in 1656, described the first member of the genus anguillula, the Anguillula aceti or vinegar eel, a familiar object, readily

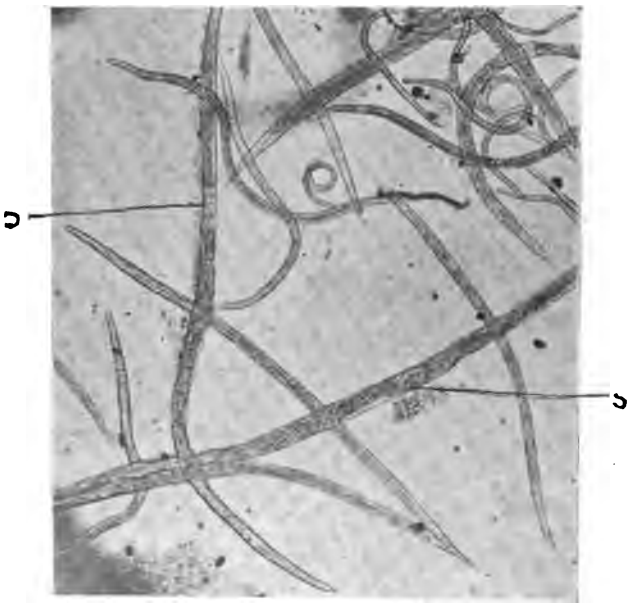
FIG. 2.

Mature male, showing hooks without fan-shaped accessory piece. Magnified 60 times.

obtained from table vinegar. From comparison with the drawings and the natural habitat of this worm it readily suggested itself that the nematode found in the urine might be the vinegar eel, its presence being accounted for by the use of a bottle that had previously contained vinegar. With this point in view, specimens of the vinegar eel were obtained by allowing weak table vinegar to remain for a few days in a warm, light place. After forty-eight to seventy-two hours, each drop of the fluid contained several eels. These varied greatly in size, depending upon their degree of maturity. The average length of the males was 1.2 mm. by 0.033 mm. The average length of

the females was 1.9 mm. by 0.06 mm. The maximum length of the females examined was 2.25 mm. Three to six ova and two to four embryos could usually be seen in the uterus of the mature females. After three to five days numerous young forms could be seen, and from this time on the number of young forms rapidly increased, the females apparently dying after depositing their ova, as the sediment consisted largely of the dead bodies and fragments of the mature worms. These young forms varied in length from 0.25 mm. to 0.7 mm.

FIG. 3.

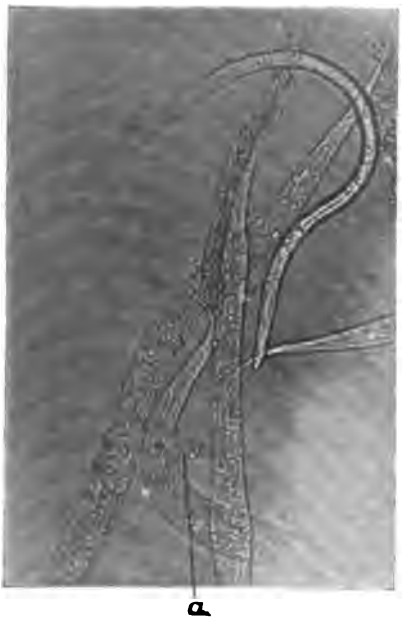


Mature female of the vinegar eel, containing embryos. Magnified 60 times.

Among the developing forms we were unable with certainty to distinguish the females until they had reached a length of 1 to 1.2 mm. Embryos were often expelled from the uterus by pressure of the cover-glass. After expulsion they would remain knotted for a few seconds, then slowly straighten out and swim actively about. These embryos were from 0 25 mm. to 0.3 mm. by 0.015 mm. The esophagus in the mature females measured on an average 0.2 mm., and proportionately shorter in the male. The posterior of the two enlargements was

top-shaped and contained three teeth arranged like the letter "Y." The intestine was continuous with this gastric enlargement, terminating at the anal opening near the posterior extremity. The tail was very pointed, and identical in this respect in both sexes. The males were provided with a pair of rather thick, double-curved spicules on the ventral surface in the anal region; projecting posteriorly from each is a fan-shaped accessory piece. In the living specimens the

FIG. 4.



Vinegar eels, showing fat-granules in the body. *a*. The protruded hooks of a male. Magnified 200 times.

spicules were always retracted, but when killed by formalin they often protruded, and then the fan-shaped accessory piece could be distinctly seen. The general color of the body from the stomach to the anal opening was dotted brownish, due to the contents of the intestinal canal. The anterior and posterior extremities are transparent, containing more or less numerous fat-like granules. The very young forms differed from the matured by having a relatively longer esophagus free from enlargements.

From a study of the above descriptions we see that the Anguillula aceti and Anguillula stercoralis bear a striking resemblance to each other in many particulars. The average length of mature males of these two species differs very slightly; apparently the Anguillula aceti are somewhat longer, as the average length of those measured equalled the maximum length given for the Anguillula stercoralis. The dimensions of the mature females of the Anguillula aceti are the same as the parasitic females of the Anguillula stercoralis. The females which develop from the embryos found in the stools are much smaller, about one-half the length of the Anguillula aceti. In internal structure and arrangement, as could be expected from members of the same genus, the resemblance is very marked. The mature males of these two species are, as far as we were able to determine, identical. The females differ in that the esophagus of the Anguillula intestinalis is practically cylindrical and without enlargements, while in Anguillula aceti the esophagus presents the same enlargements in the female as are found in the male. This difference is only present in the females found in the intestine, as those which develop from the embryos found in the stools possess the same enlargements as are found in the males. This peculiar form of the esophagus was only apparent in the embryo of the Anguillula aceti as they approached maturity, while it is reported present in all but the extremely young forms of the Anguillula stercoralis. This difference is of interest, as Teisser, in 1895, reported finding embryos in the feces which differed from those of the Anguillula stercoralis in having an esophagus free from enlargement. The position and form of the spicules, with the exception of the fan-shaped accessory piece, is identical in the two species.

Cultural experiments, conducted in order to demonstrate whether the Anguillula aceti was capable of living in acid and alkaline urine, proved the affirmative. They multiplied as rapidly in the urine as in vinegar, and after two months many living forms were still present in the urine.

A few experiments to demonstrate whether the worms could be found in the stool when vinegar was taken per os gave negative results, but further experiments in this direction are needed.

In conclusion, the following points may be emphasized:

1. The Anguillula aceti or vinegar eel resembles very closely, judging from descriptions and drawings, the Anguillula stercoralis.

2. The chief point of difference in the males of these two species is one of length, the Anguillula aceti being slightly longer.

3. The young forms differ in that the esophageal enlargement does not appear so early in the Anguillula aceti.

4. The female of the free form of Anguillula stercoralis is less than half the length of the female of the Anguillula aceti. They possess, however, the same esophageal enlargements.

5. The females of the parasitic generation correspond in length with the Anguillula aceti, but do not have the esophageal enlargements.

6. The nematode found in the urine resembles in every particular the Anguillula aceti, and we believe we are justified in these two cases in saying that the worm present was the Anguillula aceti or vinegar eel.

DISCUSSION.

DR. STILES (by invitation): Dr. Billings did not tell us whether this urine was taken with a catheter or whether it was a specimen brought to him in a bottle. In the latter event it would be possible that the bottle had previously contained vinegar. I recently examined a case showing these worms in the urine, and upon investigation we found the same worm in the vinegar which was being used in that house. Worms are frequently found in vinegar, and people swallow millions of them during the year, and yet in the numerous examinations that are made they are seldom found, so it cannot be common for them to wander from the stomach to the bladder. Still there are instances of the wandering of other worms, especially when they have gotten into a place that is foreign to them. I can recall one case reported where a severe gastritis was produced by this worm. Another possibility that occurred in my case was that the woman was a German, and one of the German methods of preventing pregnancy is to wash the vagina with water acidulated with vinegar.

The worms likely to be mistaken for this are, first, the filaria sanguinis hominis, and next the pin-worm (*oxyuris vermicularis*). The first is easily recognized, but the latter is not except by comparison with the adult pin-worm obtained from the rectum. These three cases (Dr. Billings' two and the one published from Washington) are the only ones of their kind recorded as far as I know. I was told by someone, I believe by Dr. Welch, that another such case had been reported, but I have been unable to find it.

In the article Dr. Frankland and I recently published,[1] we have given a key by which one can easily recognize all of the different forms of worms likely to be found in the urine.

DR. WELCH: The case which I referred to was one that Dr. Jacobi presented to the Association some years ago.

DR. JACOBI: In my case the worms were only found twice during an interval of four weeks, and then the urine remained normal as long as specimens were furnished to me.

[1] Stiles, Ch. Wardell, Frankland, and W. Ashby. A Case of Vinegar Eel (*Anguillula aceti*) Infection in the Human Bladder, Bulletin 35 of Bureau of Animal Industry, U. S. Department of Agriculture, Washington, 1902, pp. 35–40, Plate 4, Figs. 6–13.

A CASE OF ALBUMOSURIA OF THE PERNICIOUS ANEMIA TYPE.

By HERMAN F. VICKERY, M.D.,
OF BOSTON.

ALDOR[1] believes that the presence of albumosuria indicates some abnormality of metabolism, but that no definite diagnostic conclusions can be drawn from its absence or presence; but the prevailing opinion is that the detection of albumosuria should lead to a careful search for bone tumors.[2]

An interesting confirmatory observation is that of Dr. G. Zuelzer,[3] who reports that by administering pyrodin to dogs he produced albumosuria with marked progressive anemia, and that the bones were found filled with lymphatic tissue.

On the other hand, Askanazy[4] reported a case associated with lymphatic leukemia; and nervous symptoms associated with albumosuria are referred to by Senator.[5]

Ellinger[6] described a case of multiple lymphoma of the ribs, vertebræ, and sternum associated with a clinical picture similar to that of pernicious anemia, only without megaloblasts. During life the tumors could not be diagnosed. The typical symptoms of myeloma are paroxysms of pain referred to the bones, great deformity of the skeleton of the trunk, cachexia, and Bence-Jones' albumosuria. In the case which I desire to put on record no autopsy could be obtained. There was no distinctive clinical evidence of bone disease.

[1] Centralbl. f. in. Med., March 3, 1900.
[2] Fitz, American Journal of the Medical Sciences, 1898, vol. cxvi. p. 30; also, Hamburghser, Bulletin Johns Hopkins Hospital, February, 1901.
[3] Berl. klin. Woch., vol. xxxvii. p. 894.
[4] Deutsch. Archiv f. klin. Med., vol. lxviii. p 84.
[5] Berl. klin. Woch., vol. xxxvi. p. 161.
[6] Deutsch. Archiv. f. klin. Med., vol. lxii. Parts III. and IV.

On August 9, 1901, Mr. Edward F. applied to me because of weakness, dyspnea, and a "pumping" sensation in his head. Finding albumose in his urine, I persuaded him to enter the Massachusetts General Hospital for observation. He was there a week under my care, and the following report is the result of a study of his case.

He was a single man, aged forty-seven years; by occupation a book-keeper; a native and resident of Boston. His mother had died at the age of thirty-six years, of erysipelas, but his father, one brother, and two sisters were well. He had drunk liquor daily, and, as a young man, occasionally to excess. He had suffered from gonorrhea repeatedly, but had no knowledge of any constitutional infection.

At the age of seven years he had scarlet fever, and twelve years before entrance he had rheumatism for a week. Lately, also, he had had some stiffness between the knees and ankles. Last year it was not quite so easy for him to ride his bicycle as previously, and this year he gave it up altogether. For over a year friends had noticed that he was growing pale.

Last March he was taken with a dry cough, associated with some palpitation, cardiac pain, dyspnea, and a tight feeling about the chest. He rapidly grew very weak, so that even breathing required exertion. By June he was very dizzy on walking, and food began to distress him, and there was occasional vomiting, so that now and then he was obliged to stay in bed for a few days. Slight swelling of the feet and ankles was noticed in September, about a month after I first saw him.

He passed a light-colored urine frequently, the amount in twenty-four hours being normal, however—that is, three pints. Last winter he weighed 165 pounds, which was his best weight. When I first saw him he weighed 135 pounds, but he still appeared rather plump. His face had a pale, lemon-yellow color. The pupils were equal and normal in their reactions, but with the ophthalmoscope Dr. F. E. Cheney found slight retinal hemorrhages and a low grade of optic neuritis. The skin was moist and satiny; the tongue was moist, with a slight coat. There were a few small glands in the axillæ and the groins. The lungs were negative except for moist râles at the bases; the heart's apex was in the nipple line;

the pulmonic second sound was accented, and there was a systolic murmur in the pulmonic area.

The pulse was of small volume and low tension. The artery walls were palpable. The liver was slightly enlarged, otherwise the abdominal examination was negative; and the various reflexes were normal. While in bed there was no marked edema. Dr. J. L. Goodale found the larynx normal.

The urine was repeatedly examined, but it varied little from the condition reported by Prof. E. S. Wood, as follows: "Color, pale; specific gravity, 1016; reaction acid; urophein increased; indoxyl much increased; chlorides diminished; earthy phosphates slightly diminished; alkaline phosphates normal; urea, 1.1 per cent.; albumin, about one-half of 1 per cent., precipitated by nitric acid; by heat test an abundant precipitate forms, which dissolves on boiling and reappears on cooling—albumose. The sediment was considerable in amount, containing numerous granular casts and granular renal cells, and an occasional highly refracting cast, like a waxy cast."

The first examination of the blood was: hemoglobin, 25 per cent.; leukocytes, 6000; red globules, 1,216,000. In a count of 500 white cells the polymorphonuclears were 65 per cent.; lymphocytes, 33 per cent.; eosinophiles, 1.5 per cent.; myelocytes, 0.5 per cent. While counting these, 17 normoblasts were seen and 2 megaloblasts. The red cells stained faintly and irregularly. There was much variation in their shape and size, with a tendency to large varieties.

In a second examination the hemoglobin was 15 per cent., the white cells 6400, the red cells 1,120,000, the polymorphonuclear leukocytes were 55 per cent., lymphocytes 43 per cent., eosinophiles 0.5 per cent., myelocytes 1.5 per cent.; 10 normoblasts were seen and no megaloblasts; the character of the red cells was as before.

The patient's temperature averaged 99° F., his pulse 80 to 90, his respiration 20 to 25. He did not complain of his bony framework in any way, and nothing abnormal was detected upon examination. The X-ray revealed a slight dilatation of the heart and of the aorta, but no changes in the bones.

My colleague, Dr. W. W. Gannett, who saw the case in consultation, regarded it as one of pernicious anemia. There was so great

a tendency to vomiting and diarrhea that few drugs could be administered. Arsenic was not well borne.

After leaving the hospital, on September 12th, the patient remained in about the same condition until October 20, 1901, when he suddenly died in syncope. No autopsy could be obtained. His illness had lasted about one year.

DISCUSSION.

DR. MUSSER: In a case recently under my care of pernicious anemia, apparently secondary to chronic gastrointestinal catarrh, albumosuria was found. There was a doubtful history of hereditary syphilis, a history and manifestations of gout, a history of tobacco excess, and of an active but unhygienic life. The patient was a female, aged forty-two years. The clinical course was typically that of pernicious anemia as to blood findings, cardiovascular symptoms, fever, etc. She had pains in the bones, and particularly the right hip-joint. One week before death a small sample of urine was found by our most capable chemist, Dr. Pennington, to contain albumose. Another specimen and larger amount was requested to determine if it was of the Bence-Jones form. The patient at that time passed her urine involuntarily, and the delirium, almost mania, of the last week made catheterization impracticable.

It is also, however, of an unusual condition I wish to speak: During the latter part (two months) of life the patient suffered from air-hunger. She sighed constantly; she was always taking long breaths, and was extremely panting on exertion. In the course of a short conversation she would take long breaths at very frequent intervals.

The autopsy disclosed the usual lesions of this type of anemia. I may add, that the marrow of the bones was studied, and the ribs and the femur, which were painful during life, were critically examined, as were other bones, for bone disease.

There was, however, both macroscopically and microscopically, *fatty degeneration of the intercostal muscles and the diaphragm.* The intercostal muscles were of the appearance of the papillæ of the heart muscle so early and frequently described in this affection as "tabby-cat" striation. Fatty areas causing a mottled-yellow and red appearance were abundant, and followed the course of the muscle fasciculi. I add Dr. Steele's report of the microscopic examination of these structures:

"The *bone marrow* from the sternum and femur was a dark brownish-red. Smeared preparations show absence of fat, numbers of large marrow cells filled with neutrophilic granulations, large numbers of normal leukocytes, with a large relative number of eosinophiles, and numbers of red blood cells.

The latter are generally larger than normal, and, as a rule, are nucleated; many of them show the different stages of karyokinetic cell division.

"*The Intercostal Muscles.* Sections were embedded in celloidin, cut and stained with hemalum and eosin, and thionin and eosin. Cross sections show that the muscle bundles are much shrunken. Longitudinal sections show that in many places the fibers are pale and have lost their striations. The number of muscle nuclei are distinctly less. In many places there is a deposit of iron pigment between the muscle bundles. The degenerated bundles are granular, and apparently the process is one of fatty degeneration and atrophy. There are no basophilic cells in the sections stained by thionin. There is no increase in the connective tissue.

"*Liver.* The sections embedded in celloidin and cut and stained by hemalum and eosin show congestion of the hepatic vein and small hemorrhagic areas scattered through the acini. In many areas the liver cells are granular, have lost their outline, and are shrunken—evidently a fatty degeneration. There is no decided deposit of iron pigment.

"*Cultures.* Heart blood, sterile; pancreas, bacillus coli communis, probably agonic or postmortem invasion; spleen, sterile; liver, sterile."

DR. JACOBI: Do I understand the gentlemen to say that they believe that albumosuria in most cases draws attention to the bones? I have been under the impression that it was not a bone disease. I have seen it a number of times in pernicious anemia, particularly in those cases where there is long-continued indicanuria, and I think we will find that in grave anemias albumosuria is not at all uncommon.

DR. VICKERY: Albumosuria in small amounts is seen in other conditions, but the general impression I got from a careful reading on the subject was that the commonest cause was multiple myeloma of the bone.

PSEUDOLEUKEMIA WITH CHRONIC RELAPSING FEVER.

By HERMAN F. VICKERY, M.D.,
OF BOSTON.

Miss Margaret D., aged nineteen years, a native and resident of Cambridge, entered the Massachusetts General Hospital May 19, 1901. The family history was excellent, as also were her own previous health and habits. The catamenia, which had been regular since the age of fourteen years, had last appeared three months before admission. In August of 1900 she noticed swelling in both sides of the neck, which had steadily increased. In March, 1901, she caught cold, and a cough had persisted until entrance. The sputum was white, without blood. She had grown pale, and her voice became weaker after the attack in March. There had been no edema, hemorrhage, or diarrhea. The patient was well developed, but not well nourished. She had lost about twenty-five pounds in one year—from one hundred and twenty-two to ninety-seven pounds. The skin and mucous membranes were pale. The right pupil was slightly larger than the left, and so remained while the patient was under observation; both pupils reacted to light and accommodation, and the eyes were somewhat prominent.

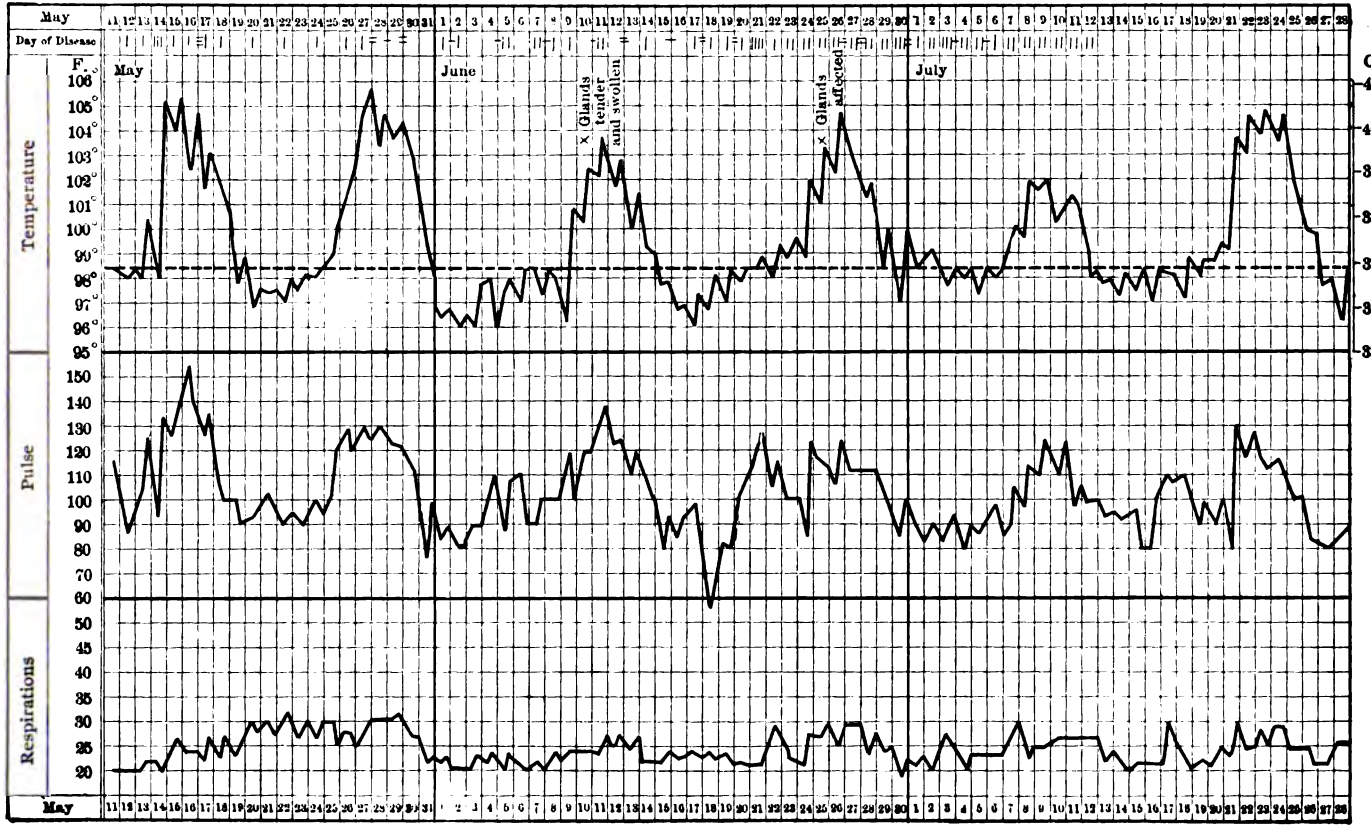
The enlargement of the neck, already mentioned, was due on the left side to glands, and on the right to a solid mass extending from the mastoid to the lower third of the neck, surrounded by separately palpable glands. None of these was attached to the skin, nor was there redness, tenderness, or fluctuation. Glands could also be felt in the left axilla and left groin. The teeth showed neglect. Thoracic examination was negative except for a soft systolic murmur, loudest in the pulmonic area, and presumably hemic. The right and left radial pulses were equal, synchronous, regular, of

low tension and small volume. The arteries were not hardened. Splenic dulness reached as high as the eighth rib, and the spleen could be just detected by palpation. The abdomen was flat and soft, and no normal masses could be detected in it. The various reflexes were normal.

The urine was of normal color, acid reaction, specific gravity 1016; of albumin there was the slightest possible trace; sugar, bile, and the diazo-reaction were absent; urea, 1.89 per cent. In the microscopic sediment a few uric-acid crystals and an occasional abnormal blood corpuscle were observed. The white cells at repeated examinations numbered, respectively, 4600, 4200, 3800, 6200, and 5000. Hemoglobin was estimated three times—at 70, 70, and 65 per cent.

The red blood corpuscles numbered 4,128,000; no abnormal forms were observed. A differential count of 500 white cells gave: polymorphonuclear leukocytes, 80.1 per cent.; large lymphocytes, 12.1 per cent.; small lymphocytes, 6.7 per cent.; eosinophiles, 1.1 per cent. No rose spots were observed. The Widal test was made twice, with negative result. The spirillum of relapsing fever was searched for in vain on three different occasions; no sputum could be obtained, after entrance, for examination for tubercle bacilli.

On July 9th, at my request, an enlarged lymph gland was removed from the neck for examination. Dr. J. H. Wright reported that it consisted chiefly of "small nuclei closely packed together in a fibrillary stroma; the nuclei vary greatly in size, and among them are eosinophilic leukocytes; also scattered among the nuclei are large cells with large nuclei. Diagnosis: mixed-cell sarcoma." On July 13 a tuberculin injection was made ($\frac{1}{100}$ gram, T. R.), with no reaction. The diazo reaction, at first negative, was faintly present on June 14 and positive on June 29 and July 24. On May 26, when the temperature was 102° to 103° F., a few râles were heard in front at the left apex, but unaccompanied by dulness or other signs. The râles did not persist. During the seventy-eight days which the patient spent in the hospital she experienced six febrile periods (see chart), each lasting six to eight days, with afebrile intervals of about equal length. During the periods of fever the neck was apt to be more swollen and tender, increasing in circumference at the level of the thyroid from 32 or 33 centi-


May
Day of Disease
May
June
July
Temperature
Pulse
Respirations
F.
C
× Glands tender and swollen
× Glands affected

meters to 36 or 37 centimeters. In the afebrile stage the patient gained somewhat, and was free from symptoms. She left the hospital July 28th, her condition being unimproved. During the last week in August she had severe pain in the back and became more or less comatose, and after an illness of thirteen months she died September 1, 1901. There was no autopsy.

Etiology. With regard to the etiology of this case the following factors suggest the possibility of a tuberculous infection: Emaciation, chronic cough, a diazo reaction, a hypoleukocytosis, and the presence at one time of râles at the left apex. On the negative side we have a favorable family history, the absence of any permanent thoracic signs, the absence of tuberculous sputum, the failure to react to tuberculin, and the microscopic appearances of the excised gland. Moreover, there was no hectic fever, and the temperature during the afebrile period did not present the marked oscillations seen in most cases of tuberculosis.

Musser[1] has shown that pseudoleukemia with recurrent fever may be associated with tuberculosis; but he has not, I think, established an essential connection between the two. W. Türk[2] states that he does not believe that pseudoleukemia, as ordinarily described, indicates a single morbid process. Pel reported of his third case[3] that at a postmortem no trace of tuberculosis could be found.

James B. Coleman[4] reports an acute case of Hodgkin's disease. During life the blood was stained and examined, and cultural experiments were made. After death various methods of staining were employed; also cultures were taken and inoculations made into the peritoneal cavity of a rabbit. All these modes of examination had a negative result. Coleman's case was not of the recurrent febrile type; but if a part, at least, of the ordinary cases of Hodgkin's disease are non-tuberculous, it seems to me easier to believe that the cases with recurrent fever are due to some as yet unrecognized organism than that they are an extraordinary manifestation of tuberculous infection.

[1] Am. Med., January 4, 1902.
[2] Wien. klin. Wochenschr., October 5, 1899.
[3] Berl. klin. Wochenschr., 1887, No. 35.
[4] Transactions of the Royal Academy of Medicine, Ireland, 1899, vol. xvii. p. 482.

DISCUSSION.

DR. STARR: Dr. Musser in his paper before this Association last year brought together a large number of cases, but it seems to me that the condition is still not generally recognized by the profession. In the month of November of last year I was called in consultation by an excellent practitioner in New York to see a patient under his care who was suffering from a condition of recurring fever as described by Dr. Musser. It was an extremely interesting case, and, as such cases are of sufficient rarity, warrants report. The patient was thirty-six years of age, of tuberculous family history, but had been fairly well until 1899, when Dr. W. T. Bull removed some glands from the neck which proved to be tubercular. In May, 1900, she began to suffer from febrile attacks lasting from seven to ten days, during which time the temperature varied from 101° to 104°, followed by a non-febrile period lasting from ten to forty days. It was thought that physical exertion, mental excitement, or painful menstruation, to which she was subject occasionally, had sufficed to bring on the fever. In October, 1901, she was seen again by Dr. Bull, and was again advised to have some glands removed from the neck. This time a careful examination of the glands showed no tuberculous lesions, nor were they sarcomatous in nature. The temperature chart from November 25th to January 4th shows the occurrence of two febrile attacks (with temperature from 99° to 104°) of ten days' duration each, during which physical examination showed nothing except a slight splenic enlargement. There was no evidence of abnormality in the lungs and no enlarged mediastinal glands. A blood examination was made during the attack of fever when the temperature was at 102°, and showed red cells, 4,040,000; white cells, 5800, and hemoglobin, 90 per cent. Differential count showed polynuclear neutrophiles, 72 per cent.; large mononuclear leucocytes, 20 per cent.; small mononuclears, 7 per cent.; eosinophiles, 3 per cent. The diagnosis being perfectly clear as a case of Ebstein's disease, and being wholly out of my line, I retired from the case. I hear that Dr. Kinnicutt was called to see the patient in February, and he will continue the history.

DR. KINNICUTT: I saw the patient in February of the present year, and will simply present the temperature charts taken since that time. There have been three periods of pyrexia, of ten, thirteen, and nineteen days, and three periods of apyrexia, of five, seven, and eight days. The temperature rises slowly, much as it does in typhoid, and then as slowly descends. A very careful examination of the patient when I last saw her shows progress of the disease since she was examined by Dr. Starr. The glands in the neck and axilla were enlarged; the spleen was markedly enlarged, its surface hard and irregular; the liver was slightly enlarged, and there was evidence of movement of the glands of the anterior mediastinal space.

It seems to me that there are two views possible regarding this condition. One is that it is an infective disease occurring both in an acute and chronic form, with an organism as yet undiscovered. The other is that under the names of lymphadenoma has been grouped a number of cases that present dissimilar pathologic processes, although clinically resembling each other.

DR. MUSSER: There is no doubt a large number of cases of so-called Hodgkin's disease are really tuberculous. To say they are not tuberculous, the burden of proof must rest with the pathologist. One examination of any purulent exudate and histologic examination of one gland is not enough. Repeated examinations must be made, and, as a final court, inoculation experiments must be resorted to. Of course, the tuberculin test is to be employed.

The fever has been referred to. In the fairly large number of cases which I collected last year fever was present in cases which were undoubtedly tuberculous, or in cases of lymphosarcoma, although styled Hodgkin's disease. It seems, therefore, it is not the specific process which gave rise to the fever, but rather fever occurred because a morbid process was in progress in lymphatic structures. Ebstein's fever is not a symptom of any one disease unless it be tuberculosis. It is not a symptom of Hodgkin's disease. It is a symptom of adenitis, which may be tuberculous, or may be a sarcomatosis, or may have other causes.

The nomenclature is unfortunate. It seems as our knowledge of specific causes widens we can say definitely the form of chronic enlargement of the lymphatic glands known as Hodgkin's disease is of most infrequent occurrence, and one is privileged to see very few if any case corresponding to the two cases of Hodgkin's group which alone are separated from tuberculosis or sarcoma.

Personally, I believe adenitis, which is described as Hodgkin's disease, is nearly, I should say always, infectious and usually tuberculous or syphilitic, or it is a form of lymphadenoma. The symptom group of Hodgkin's disease is not due to the adenitis, except when the symptoms are mechanical, but to some factor underlying which causes the adenitis.

REPORT OF A CASE OF SEVERE, PROBABLY PERNICIOUS, ANEMIA WITH MARKED GENERAL AND CORONARY ATHEROMA, IN WHICH MANY EVIDENCES OF ANEURYSM WERE PRESENT WITHOUT ANATOMIC EXPLANATION FOR THEM.

By ARTHUR R. EDWARDS, M.D.,
of Chicago.

J. W., a Canadian laborer, aged thirty-one years, married, entered Ward Six in my Cook County Hospital service March 3, 1897. His previous history was somewhat meager. Eight years previously he had a single venereal sore, two or three months after which he had rheumatism, and somewhat later an attack of pleurisy, the location of which he could not recall. An alcoholic and tobacco history was elicited.

As to his present history, he had grown weaker, but had not lost any great amount of flesh. Some pain had existed for weeks or months over the lower left chest. The appetite had declined, but anorexia was not absolute, nor did it concern any special variety of food. He vomited once, and eructations of gas were frequent. There had been some slight dyspnea, increased by exertion and the erect posture. The skin for a week had been somewhat yellow, and the urine was dark, but the bowel movements were not noted. Direct questioning developed no other points.

Physical Examination. The patient lay in a somewhat listless state. His breathing was moderately accelerated, ranging between 25 and 32 respirations a minute. The skin and mucosæ were distinctly yet not deeply icteric; the tongue was covered with a yellowish-white fur; the hair was somewhat thin. Examination in other respects was negative regarding the head, scalp, ears, eyes, and throat. The lungs were wholly negative except that respiratory excursion was absent over the left lower lobe, laterally and posteriorly. The peripheral arteries pulsated actively, yet arterial tension was low. The initial pulse-rate ran between 90 and 112. The radials and brachials alone were tortuous and rigid to the finger. No inequality in tension nor in the size of the pulse-wave was noticed in any of the arteries, including the femorals.

The heart was normal in its outlines, save that the left border and apex-beat were found in the left nipple line. A soft blowing systolic murmur was

heard with equal distinctness over the pulmonic and mitral areas, and the second aortic tone was loud and almost metallic.

Over the lower left chest was observed a diffuse and most distinct pulsation which, as the patient lay on his right side, extended horizontally from the lower angle of the left scapula around the chest into Traube's space and the epigastrium, and in a downward direction to a point distinctly below the left costal arch. The pulsation was vigorous and distinctly expansile to both the eye and the hand. A systolic bruit was heard over the pulsating area, but was most clearly audible over the left chest behind. No thrill was detected at any time.

The liver's edge was barely palpable on deep inspiration, was even, and of normal resistance. The spleen could not be felt; otherwise the abdomen was negative. The urine was 1020 c.c.; specific gravity, 1016; a trace of albumin; urea, 1.7 per cent.; no sugar, no peptone, etc.; a moderate number of small granular casts were found.

The nervous system was negative.

The stools were not acholic.

The patient was demonstrated in my clinic as aneurysm either high in the abdominal aorta, or possibly low in the thoracic aorta. Dr. Robert B. Preble, of the attending staff, also examined the case and demonstrated it as aneurysm. When in the clinic the pulsation could be clearly seen twenty or thirty feet, and its striking expansile throb was demonstrated by pasting on the anterior and posterior surface of the lower chest small pieces of bent paper, which were widely separated with each cardiac systole. This experiment was performed to demonstrate the expansion to the eye rather than to the hand of the student. The blood was not examined at first, but a few days before the patient's death his temperature, which had occasionally reached 100° and 100.6° F., fell to 97° by mouth; his pulse became thready and could scarcely be counted. The respiration became rapid and shallow, with all of the classic symptoms of collapse. Upon reaction the pulsation was less distinct, and a decided anemic appearance then was first noted, possibly having been obscured by the previously icteric hue, which had now largely disappeared. Examination of the femoral and other vessels was carefully made, with the thought that retroperitoneal or other rupture had occurred. The femorals were equal and synchronous with each other and the radials, etc. The blood showed 5000 leucocytes to the cubic millimeter, a differential count of which revealed normal relations. The red cells numbered 1,400,000, and the hemoglobin by Fleischl's instrument registered 32 per cent. In the stained preparation the red cells varied but little in size and dimension. There was not much poikilocytosis. A large number of nucleated red corpuscles were seen, the great bulk of which were normoblasts, few megaloblasts being detected.

The patient collapsed again, and died rather suddenly March 21st, eighteen days after admission.

The *clinical diagnosis* was formulated as follows: 1. Arteriosclerosis. 2. Abdominal aneurysm, probably pointing toward the diaphragm. Little

stress was placed upon the mere fact of the pulsation, but the perfectly clear expansion of the pulsation seemed to establish the diagnosis of aneurysm beyond doubt, with rupture explaining the collapse. 3. Dilatation of the left ventricle. 4. Catarrhal icterus. 5. Acute secondary anemia. The possibility of pernicious anemia was discussed and considerable uncertainty was experienced, still it seemed to all who examined the case that the evidences of aneurysm followed by collapse from rupture and sudden death outweighed all other considerations.

Postmortem, No. 104, March 22d, one day after death, attended by Drs. Preble, Brown, Hammond, Hunter, Champlin, Smith, Humiston, McGrady, Kirby, and the writer. Some emaciation; well-marked rigor mortis. The pericardium contained four grams of clear serum. The heart weighed 600 grams; the endocardium presented the tabby-cat appearance; the myocardium was very pale. Very small yellow plaques were found at the base of the mitral valves and in the beginning of the aorta.

In the left coronary artery, one inch below its origin, was a long plaque or series of plaques of yellow color, hard, some elevated and the size of a pinhead, while others were diffuse and larger. Similar changes were found in the right coronary one and a half inch below its origin. Over the entire length of the abdominal and thoracic aorta were scattered small yellow areas, some of which were hard, rough, elevated, breaking with a distinct sound, and almost nodular.

Nowhere were there any bulgings nor aneurysm of the aorta. Similar changes existed in the common iliacs, external and internal iliacs, the femoral arteries, and a few of the larger branches of the latter. The nose, larynx, and trachea were negative. The bronchial glands were slightly enlarged and on section anthracotic. The mediastinum was negative. The right pleural cavity contained 300 c.c. of clear serum, and no adhesions existed. A few old, thin adhesions were found over the left apex, and the base of the left lung was adherent by well-organized tissue to the chest wall and the diaphragm. The adhesions were edematous. Above these basal adhesions was a small amount of clear serum. The right lung weighed 530 grams, the left 660. The lungs floated, crepitated throughout, and on section appeared light gray, a frothy yellow serum being readily expressed, particularly from the left lower lobe. The tongue and the pharynx were negative.

The esophagus and stomach were exceedingly pale, as was the mucosa of the small and large gut, save for some hypostatic postmortem discoloration. Small, hard plaques similar to those found in the aorta were seen in the superior mesenteric artery and its larger branches. The peritoneum was smooth, and the abdominal cavity contained no fluid. The bile ducts were patent and the gall-bladder slightly distended with somewhat viscid bile. The liver weighed 1940 grams, and its surface was light red and mottled. No adhesions were found, and the liver's edge was smooth and sharp. Its consistence was firm, and on section contained but a moderate amount of blood. On section the lobular markings were fairly distinct, the center showing red and the

periphery light. The pancreas was negative, weighing 120 grams; the spleen weighed 180 grams, and there were some perisplenitic adhesions, but to the diaphragm only. The organ was dark purple in color, and the parenchyma soft and friable. The left kidney weighed 200 and the right 160 grams. The capsule was easily stripped, leaving a smooth, very pale, and slightly mottled surface. The section was very pale, the cortical markings were obliterated, and the cortex and medullary portion were as 1 to 3. The pelvis, ureters, bladder, prostate, seminal vesicles, and urethra were negative.

The brain weighed 1650 grams, and its examination was wholly negative, especial attention having been directed to the bloodvessels. The spine and cord could not be examined. The long bones could not be examined, but the section of the sternum showed the reddish jelly-like marrow seen in pernicious and other severe anemias.

Anatomic Diagnosis. Atheroma of the coronary arteries, mitral valves, aorta and its main lower branches; left ventricle hypertrophy and dilatation; fatty degeneration of the myocardium; pulmonary edema; partial left adhesive pleuritis; chronic nephritis, acute splenic tumor; perisplenitis; marked anemia of the alimentary tract, etc.; pernicious anemia (?).

The case presents no remarkable pathologic features. The vascular changes were very marked for a person aged thirty-one years, and may be referred with some degree of correctness to syphilis. While the blood findings were not exactly characteristic of pernicious anemia, still they corresponded fairly well with the subacute or milder recurrent type of pernicious anemia as described by Cabot and others. The exact cause of the collapse, considered by us as due to aneurysmal rupture, which led to sudden death in its second occurrence, may have been due to the extensive bilateral coronary disease or to this cause combined with the profound anemia.

The chief clinical interest of the case centers in the pulsation. The pulsation was extensive, attended by a bruit, abdominal as well as thoracic, and markedly expansile.

At first thought it might seem that the pulsation resembled Broadbent's sign, but the pleural adhesion was purely basal, and there was neither pericardial, synechia, nor indurative mediastinitis. When a pulsable movement, says Broadbent, is seen in the lower posterior chest it may appear at first sight to be expansile, but on more careful scrutiny it is found that there is a tug upon the false ribs during the systole and a sharp rebound during the diastole, etc.

It has been impossible for me to look over the literature bearing upon this unique case for a lack of a title covering its phenomena.

Personal inquiry of a number of experienced clinicians, as Prof. Osler, has not developed any similar instance.

The pleural adhesions and lack of respiratory excursion at the base of the left lung was noted clinically, but did not excite any remark, since among the lung changes incident to aneurysm, pleurisy with effusion, adhesive pleurisy, lung induration, etc., have been repeatedly described by writers on aneurysm since the classic work by Stokes. The adhesions were thought to be either due (1) to aneurysm near the diaphragm, or (2) to mere coincidence. Nothing suggested pulsating neoplasm of the lung or pleura. A pulsating pneumonia as described by Graves was merely mentioned in the clinic as one of the causes of thoracic pulsation, as were pulsation of the liver and spleen in Basedow's disease, aortic and tricuspid regurgitation as rare causes for abdominal pulsation. Mention was then made of the empyema pulsatile (Aran), the pulsating empyema of Stokes, and the empyema necessitatis pulsans of MacDonnell.

Dr. J. C. Wilson has reviewed with great care the subject of pulsating pleural effusions.

The literature of pleuritis pulsans brings out the fact that most instances (about 92 per cent.) are left-sided. A review of the causes suggested concerns—

1. The theory of Traube, which referred the pulsation to the condition of the heart and pericardium.

2. Comby's theory placed stress upon adhesions to the pericardium and compression of the lung.

3. Féréol's explanation was pneumothorax with a large effusion, these conditions being imperative.

Wilson's conditions: (*a*) Some paresis of the intercostal muscles, as results from a long-standing pleuritis; (*b*) local necrosis and perforation of the parietal pleura (empyema necessitatis); (*c*) pneumothorax; (*d*) atelectasis of the lung, which is in relation with and adherent to the pericardium.

Aneurysm has often been thought of, but the statement constantly recurs that it can usually be excluded, except when an encysted empyema lies close to the heart. Among the conditions just named practically the only one in our case was the pleural adhesions over the base of the left lung. I have been able to reach no satisfactory explanation of this pulsation, although the active arterial pulsation

might have been propagated by means of the adhesions to the chest and by means of the perisplenitic connective tissue to the abdomen. This suspicion, however, in no way accounts for the *expansile character of the pulsation*, which of yore has been held to invariably (Ref. 14, 15) exclude dynamic pulsation.

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DISCUSSION.

DR. PEABODY: I simply rise to say that it seems to me that the explanation offered as a possible one really cannot be regarded as entirely satisfactory, because it happens to all of us to find extensive adhesions of the lower lobe of the left lung and of the spleen without such phenomena as these. It would seem to me likely that some other explanation must be the true one.

DR. JACOBI: The doctor did not specify the condition of the hepatic and splenic arteries. I have seen large hepatic aneurysms that might be the cause in such a case.

DR. EDWARDS: All of the arteries were normal in this case.

DR. LAFLEUR: I have had exactly the same experience as Dr. Edwards within the last two months. The case was one of secondary anemia, and the phenomena were those usual to aneurysms. The pulsation was exactly what he describes, and there was in addition a paralysis of the left vocal cord. We were mistaken in our diagnosis, as the autopsy showed no aneurysm, but an ulceration of the stomach, which had not been recognized. It emphasizes

the fact that pulsations in the lower half of the chest or the upper half of the abdomen is a notoriously uncertain sign.

DR. COHEN: I did not understand that any fluoroscopic examination was made in these cases. Of course, I know that fluoroscopic examinations in the abdomen cannot always be depended upon; yet recently in the case of a young lady referred to me from Virginia with an ordinary anemia, not pernicious; with marked pulsation in the abdomen; with a bruit, but no thrill —the diagnosis of abdominal aneurysm having been made at home—the skiagram proved distinctly the absence of aneurysm.

DR. SHATTUCK: An amusing case comes to my mind in this connection. A number of years ago a man came to me from Maine for examination, and I told him I found nothing. "Well," says he, "my doctor tells me that I have an abdominal aneurysm, and that I must lie absolutely still for six months." I examined him again, and said I could not find it; and then he told me that his doctor had given him a list of five physicians in Boston, and told him that if they did not find an aneurysm he would pay all his expenses and fees. The man has remained absolutely well, and shows the risk of making such an offer.

DR. EDWARDS: The interesting point, it seems to me, reducing all the facts of the case to the simplest terms, is this, that we had a dynamic pulsation in the lower part of the chest and abdomen which was expansile.

THE PATHOLOGY OF LABIAL AND NASAL HERPES AND OF HERPES OF THE BODY OCCURRING IN ACUTE CROUPOUS PNEUMONIA AND THEIR RELATION TO THE SO-CALLED HERPES ZOSTER.

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(From the Pathological Laboratory of the Lakeside Hospital, Cleveland.)

Our knowledge of herpes zoster was very much extended by the recent contribution of Head and Carpenter (*Brain*, Autumn, 1900). These authors showed among other things (1) that herpes zoster, in eighteen cases at least, is associated with destructive and usually inflammatory changes in the sensory ganglia (posterior root or Gasserian) corresponding to the nerve supply of the part affected with herpes; (2) that in recent cases, before the eleventh day, degenerative changes are not demonstrable in either the peripheral nerves, the posterior root fibers, or the central nervous system; (3) that in cases examined after the lapse of this period degenerative changes are present in these structures and apparently correspond to the affected areas in the ganglia. Their work was based upon the study of twenty-one cases in all stages of the eruption. They state that before their own work there were only two well-reported autopsies on cases of herpes ophthalmicus (Wys and Sattler) and five satisfactory reports on zoster of the trunk (Lesser, Chandelux and Dubler). Von Bärensprung's oft-quoted case is classified as unsatisfactory, because, though he noted the occurrence of hemorrhage into a ganglion, he failed to mention to which of the three ganglia removed he alluded.

While this valuable communication has placed our knowledge of herpes zoster on a substantial basis, it is clear that more light is needed upon the etiologic factors concerned, as well as upon the

identification and classification of the various types of herpes. In order to clearly understand our present knowledge on the subject, the following summary of the main facts may be helpful.

There are a number of clinical and apparently several anatomic types of herpes: herpes zoster involving the neck, trunk, and extremities, following the distribution of the spinal posterior root ganglia; herpes ophthalmicus following the distribution of the first division of the fifth or trigeminal nerve (Gasserian ganglion); herpes labialis et nasalis probably following the distribution of the second and third divisions of the trigeminal nerve, but unsupported at this time by anatomic observations; and herpes genitalis, commonly believed to be due to local irritation, and not known to be associated with any lesion of the nervous system.

The herpes facialis, labialis, nasalis, and genitalis are classed by Hartzell (*Reference Hand-book of the Medical Sciences*, vol. iv., 1902) as herpes simplex in contradistinction to herpes zoster of the neck, trunk, extremities, and ophthalmic area (herpes zoster ophthalmicus). These latter forms of herpes have been shown to be identical, in that they are associated with the same lesions of the nervous system, especially those of the sensory ganglion; the changes in the skin are believed to be the same.

It seems further to have been conclusively demonstrated that the lesions of the skin are secondary to the primary changes in the corresponding sensory ganglia, which in turn may be brought about by a variety of causes. The cases, however, may be classified into the primary or spontaneous herpes zoster in which the affection is apparently primary, and not due to any evident preceding infection or injury, and the secondary form in which there is more or less clear evidence that the disease occurs as the sequel or complication of some antecedent affection, as pneumonia, cerebrospinal meningitis, etc., or to injury.

Our knowledge of the changes in the skin in the various clinical forms of herpes is far from satisfactory. Not until a sufficient number of careful observations upon the histologic changes in all the stages of each variety of herpes are available will we be in a position to compare critically the processes, and perhaps distinguish clearly the different forms. Suffice it to say for the present, that after comparing the histologic appearances described by various authors of

the changes in herpes zoster, herpes labialis, and genitalis (all available) with those of my own cases herewith reported, and making due allowances for the different stages of the processes studied, I am not able to find any constant distinguishing characters by which the skin lesions of the various clinical forms of herpes may be separated.

I have recently had the opportunity of studying two cases which throw some light upon several points of importance in the pathology of herpes. The first case occurred in the private practice of my friend Dr. Edward F. Cushing, who recognized its interest and importance and obtained the autopsy. I take this opportunity of expressing my thanks to Dr. Cushing for the autopsy, and for the use of the clinical history of the case. This case illustrates the causal relation between acute infections and herpes zoster, and emphasizes the identity of the lesions of the skin and nervous system in primary and secondary herpes of the trunk.

CASE I.—*Summary.* Bronchitis; acute croupous pneumonia of both lungs; herpes zoster of the left side, distributed on the back and side (sixth dorsal) and the abdomen (eleventh dorsal); congestion and hemorrhage into the capsular and interstitial tissue at one side of the eleventh left dorsal ganglion, with slight cellular infiltration and destruction of a few ganglion cells; amylaceous and hyaloid bodies in another portion of the same ganglion; slight chronic and acute interstitial nephritis; acute parenchymatous and interstitial hepatitis; acute splenic tumor; old pericardial adhesions; hypertrophy and dilatation of the heart; fibromyoma uteri.

Clinical History. Miss T., aged sixty-three years, had not been well for about one year. On October 10, 1901, she was taken sick with a cold in the head, which a few days later was followed by bronchitis. She then developed pneumonia of the lower lobe of the left lung. Later the whole of this lung became consolidated. On the morning of October 24th physical signs of consolidation of the lower lobe of the right lung were observed. Coincident with the consolidation of the lower lobe of the left lung there developed well-marked herpes zoster in the mid-dorsal region of the left side, extending from the middle line in the back to about the anterior axillary line, corresponding to Head's sixth dorsal area. During the last two days of life a similar eruption appeared on the abdomen in the left umbilical and iliac regions (eleventh dorsal area; see autopsy protocol). Albumin was present in the urine. Death occurred at 2.30 P.M. October 24, 1901. The autopsy was begun six hours later.

The autopsy was done hurriedly and under difficulties at the home of the patient.

The body measured 160 cm. long, was sparely built except over the abdomen and lower portion of the back, where there was considerable amount of

fat. The body was cold; rigor mortis moderate. There were a few reddish, discolored areas on the outer aspects of the legs. On the left side of the abdomen, situated in the outer and lower portion of the left umbilical and the upper portion of the left iliac regions, there was an area the size of the palm of the hand, studded with scattered pale red or gray areas from 3 to 6 or 10 mm. in diameter. Some of these areas were elevated and covered with dry, grayish-red material, while others showed a distinct loss of epidermis. No typical vesicles containing fluid were to be found, but the areas had the appearance of dried vesicles. In distribution this area corresponded with Head's eleventh dorsal area. A similar but narrow area extended from the middle line in the mid-dorsal region as far as the anterior axillary line, under the nipple, corresponding to Head's sixth dorsal area. The areas here were larger, and the process appeared older than that on the abdomen. No other lesions were found upon the surface of the body. There was no facial herpes.

Chest: The chest was fairly well shaped, the muscles and fat rather wasted.

Both pleuræ were free from adhesions, and the pleural cavities contained no fluid. The visceral pleuræ over considerable areas were covered with a thin layer of fibrin and were red and lusterless.

Right Lung: The apex was free from puckering and thickening. The upper lobe on section was congested and markedly edematous. The whole of the middle and a large part of the lower lobe were consolidated, airless, and of a grayish-red color and granular appearance. The mucous membrane of the bronchi was congested.

Left Lung: The whole lung was consolidated, airless, of a gray or grayish-red color, and granular appearance. The bronchial mucosa was congested. The bronchial glands were pigmented, but free from tubercle.

Heart: The pericardium was adherent to the diaphragm over a large area. Firm fibrous adhesions obliterated the pericardial sac. The walls of both ventricles were thickened. The valves, the coronary arteries and veins, as well as the aorta and large arteries, were normal. The myocardium was pale, otherwise normal. The heart weighed 400 grams.

Abdomen: The muscles and fat of the abdominal wall were of ordinary appearance. The left lumbar region was prominent. The stomach was distended with gas, the large and small intestines contracted.

Liver: The liver was of ordinary appearance and size. The edges were rounded, the surfaces smooth, consistency not increased. On section the lobules were visible, the surface pale. The gall-bladder and bile-ducts were negative.

Spleen: The spleen was twice the ordinary size. On section it was of a grayish-red color, the trabiculæ and Malpighian bodies visible, consistency decreased.

Kidneys: The kidneys were of about the same size and appearance. The capsules were adherent in places, the surfaces were somewhat granular and marked by a few old scars. On section the consistency was somewhat

increased, the surfaces pale, the cortices thinner than ordinary. The arteries, pelves, ureters, bladder, and adrenals appeared normal, as did the stomach and intestines.

The ovaries were small and tough to the touch. The uterus was considerably enlarged; the body was the seat of a globular fibroma the size of an orange.

Nervous System: The brain could not be examined, and the examination was confined to the lower portion of the spinal cord. From the tenth dorsal segment downward with the cord the eleventh and twelfth dorsal and first lumbar posterior ganglia of both sides were removed. It was not possible to go higher in the time available for the examination. There was an excess of cerebrospinal fluid, which, however, was quite clear. The meninges were normal in appearance. The cord showed no lesions on section. The ganglia showed no macroscopic lesions, and no hemorrhages were found about the posterior roots or the nerves going from the ganglia.

Portions of the various organs, including the cord and the ganglia, were hardened in Orth's fluid. The ganglia were transferred to 96 per cent. alcohol after a few hours. Portions of various organs, including the skin, were also hardened in Zenker's fluid.

Bacteriologic Examination. Cover-slip preparations from the lungs and pleuræ showed lanceolate diplococci in capsules. Cultures on blood serum and on glycerin-agar from the lungs, heart's blood, liver, spleen, kidneys, and cerebrospinal fluid remained sterile.

Histologic Examination. Lungs: Sections from both lungs showed well-marked croupous pneumonia, with lanceolate diplococci in the alveolar exudate.

Liver: There was well-marked fatty degeneration of the liver cells, congestion of the capillaries, with marked round-cell infiltration about many of the portal systems. No focal necrosis and no bacteria were found in suitably stained sections.

Kidneys: There were scattered areas of chronic glomerulitis, with thickening of the capillaries and of Bowman's capsule, with but little atrophy of the neighboring tubules. The epithelial cells of the convoluted tubules showed cloudy swelling. With no apparent relation with changes in the glomeruli or tubules, there were numerous areas of round-cell infiltration. Most of these cells were of the plasma cell type, but some were lymphocytes. There was no necrosis of the renal epithelium and no abscess formation. No bacteria were to be found.

Skin: Sections were made through both areas of herpes, and, with the exception that the lesions were more extensive in the older lesion (sixth dorsal region), the changes were the same. There were few unbroken vesicles, but in most places the surface of the lesion was covered with amorphous and fibrillated fibrin, containing a larger or smaller number of desquamated, swollen, and often disintegrating and necrotic epithelial cells. Some of these cells had undergone coagulation, and others liquefactive necrosis. In some places the cells of the deeper layer of the epidermis were markedly

swollen, vacuolated, and evidently dropsical. In the fibrin and among the epithelial cells on the surface there were variable, often great, numbers of polymorphonuclear neutrophiliar leukocytes. In some places there were cavities formed by the elevation of the superficial or subcorneal layer of epithelium. These were of considerable size in places, but were not numerous. Other small vesicles occurred in the exudate, their walls being formed by necrotic cells. Still other vesicles were between the epidermis and the underlying papillary layer. These were always small. In many places the papillary layer was exposed by the total destruction of the epidermis, and was covered by the exudation. In the papillæ and in the upper layer of the corium the veins and capillaries were markedly dilated, and in places there was hemorrhage either into the tissue or upon the surface. The papillæ and the upper layers of the corium showed other intense changes, coagulation necrosis, with hyaline and fibrinoid changes, nuclear fragmentation, and infiltration, with large numbers of polymorphonuclear neutrophiles, lymphocytes, and some plasma cells. Here and there a few eosinophiles were to be seen. This cellular infiltration was both diffuse and along the bloodvessels.

Many of the sweat glands and hair follicles were swollen and distended with leukocytic and serous exudate. The epithelial cells were commonly swollen, granular, and often desquamated and necrotic. About many of these glands there was well-marked leukocytic infiltration, a few of the cells being eosinophiles. Scattered collections of leukocytes were also seen in the deeper layers of the skin. No bacteria were to be found in any of the lesions in sections stained by Weigert's fibrin method or with eosin and methylene blue. The whole appearance of the lesion points to rapidly necrotic and exudative processes.

Posterior Root Ganglia: Sections were cut of the eleventh and twelfth dorsal and first lumbar ganglia of both sides, and stained by Nissl's, Weigert's, and Marchi's methods, as well as with methylene blue and eosin and hematoxylin and eosin. Sections from all the ganglia studied, except the eleventh dorsal of the left side, were entirely normal.

In sections of the latter ganglion changes were found in two places: (1) at one side of the ganglion, about midway of its length, and (2) at the peripheral end.

1. In the sections cut transversely through about the middle of the ganglion, at one side, there was considerable hemorrhage, with pigmentation, into the capsule. In some of the sections corresponding to the area of capsular hemorrhage there was just beneath the capsule marked congestion of the capillaries and interstitial hemorrhage between the ganglion cells. In several sections small areas of cellular infiltration about destroyed ganglion cells were found. The ganglion cells elsewhere stained well and appeared normal.

2. At the peripheral end of the ganglion there were a number of amylaceous and hyaloid bodies, both singly and in groups, of the size and shape of ganglion cells, and lying in spaces similar to ganglion cell-spaces. Many of these bodies were finely granular, some of the granules staining pink with

eosin, and others blue with toluidin blue. Many bodies stained diffusely pink with eosin, and some diffusely blue with blue dyes. In some a central nucleus was apparent, and many showed a concentric arrangement. In a few places hyaline masses were made out in lymph spaces and in blood capillaries. Hyaloid and amylaceous bodies were also found in unmistakable lymph and bloodvessels. The question whether or not some at least of these bodies represented degenerated nerve cells is difficult to answer. From careful study I am convinced that some of them were formed and lie in nerve-cell spaces. No lesions of the peripheral nerve, the posterior nerve roots, or the spinal cord could be made out.

The interpretation of the pathologic changes of the above case appear to be as follows:

Acute croupous pneumonia following bronchitis, with the ordinary parenchymatous changes of the liver and kidney common in such cases, with the addition of acute interstitial hepatitis and nephritis; a herpetic eruption of certain cutaneous areas, the spinal root ganglion corresponding to one of which areas was shown to be the seat of definite lesions, *i. e.*, congestion and hemorrhage of both the capsule and a small area of the interstitial tissue of the ganglion, with cellular infiltration about a few degenerated ganglion cells, with hyaloid and amylaceous bodies in another portion of the ganglion.

It seems fair in the light of our present knowledge to attribute these various lesions to the toxins of the pneumococcus.

The failure to find degenerative changes in the cord, the posterior roots and the peripheral nerve is in accord with observations of Head and Carpenter, who did not find changes in these organs in a case of herpes dying on the eighth day. They were present in a case dying on the thirteenth day.

Including the five cases of Lesser, Chandelux and Dubler with the sixteen cases of Head and Carpenter, there are twenty-one well-studied cases of herpes zoster of the trunk in which definite destructive lesions have been demonstrated in the posterior root ganglia corresponding to the distribution of the herpetic eruption. Two of the twenty-one cases of Head and Carpenter involved the head, in one case the ganglion was not removed, and in two others in which death took place in 139 and 240 days, respectively, no lesions of the nervous system were found. In all nine of the acute cases, three to sixteen days after the appearance of the eruption, definite and unmistakable ganglionic lesions were found. Of these cases two had had

acute infections (cystitis with retention of urine in paraplegia and acute bronchitis and tubercular pneumonia). In the twelve chronic cases in which death occurred in from 57 to 790 days after the herpes, the sensory ganglia corresponding to the distribution of the eruption showed well-marked chronic changes.

Our next case shows that the changes in the skin and Gasserian ganglion in herpes of the lips and nose in pneumonia are identical with those occurring in herpes ophthalmicus, and in the skin and posterior root ganglia in both primary and secondary herpes zoster of the trunk. It is also, curiously enough, apparently the first case of herpes of this region in which changes have been sought for in the Gasserian ganglion.

CASE II.—*Summary.* Acute croupous pneumonia in a bartender, aged forty-one years. Death on the sixth day of the disease. Two days before death well-marked herpes of the upper lip and the nose, being much more extensive on the left side.

Autopsy showed acute croupous pneumonia (gray hepatization), involving the whole of the left lung, with fibrinopurulent pleurisy of the left side, edema and congestion of the left lung. Chronic fibrous, obliterative pleurisy of the right side. Herpes of the upper lip and nose, most marked on the left side. Congestion of the areas about the origins of the superior maxillary branches of both Gasserian ganglia. Hemorrhage into the capsule and tissue, with interstitial cellular infiltration and compression and degeneration of the ganglion cells near the origin of the superior maxillary branch of the left Gasserian ganglion. A few small areas of cellular infiltration in the same part of the right Gasserian ganglion. Marked congestion of the veins of the neck and brain and of the cerebral sinuses. Pneumococcus in the right lung and left pleura.

Clinical History. For permission to use the clinical history of the following case I am indebted to the courtesy of my colleague, Dr. J. H. Lowman, in whose service in the Lakeside Hospital the patient was admitted February 6, 1902, complaining of pain in the right side of the chest, cough, and fever.

The patient was a male, aged forty-one years, white, and a barkeeper by occupation. His family history was without present interest. Personal history: He did not recall having ever been sick before, and denied having had diphtheria, scarlatina, rheumatism, pneumonia, pleurisy, syphilis, and gonorrhea, typhoid and malarial fevers. Some time ago he injured his right temple by a fall, but the wound healed promptly and was followed by no clinical symptoms. He drank beer and whiskey to excess at times, and also used tobacco. He had been a barkeeper for twelve years.

Present Illness. He got his feet wet the night of February 8th, and waked up the next morning with severe pain in the right side of the chest, but did not have a chill.

On admission he had the physical signs of consolidation of the lower portion of the right lung. The left lung was clear; the spleen was enlarged. Examination of the other organs was negative. The leukocyte count on February 8th was 19,000, and on February 9th 13,000 per cubic mm. On February 9th, the fourth day of the disease, there appeared a well-marked vesicular eruption over the upper lip and the outer surface in the vestibule of the left side of the nose. This eruption on the lip and the outside of the nose extended somewhat to the right side of the median line. The sputum contained lanceolate diplococci. By February 11th the whole right lung was consolidated, and numerous moist râles were to be heard over the left lung. The patient was delirious. Death occurred suddenly at 1.15 P.M., February 11, 1902, on the fifth day of the pneumonia, and the beginning of the third day of the herpetic eruption.

Autopsy one hour after death. Body warm; no rigor mortis; body 165 cm. long, well built and well nourished. There were no marked scars or wounds on the body. On the upper lip, involving both mucous and skin surfaces, there were a number of dried crusts surmounting slightly climated areas with red margins. These areas varied from 2 to 5 mm. in diameter. Similar papules and dried vesicles were present on the skin of the vestibule and external surface of left side of the nose. Altogether there were from fifteen to twenty such areas. Several similar lesions were also found to the right side of the median line of the lip and nose. No other herpetic eruptions were to be found on the body.

Nervous System: The veins of the dura and pia arachnoid and all the sinuses were markedly congested. The pia arachnoid was smooth and glistening. The structures at the base of the brain were normal. The brain on section showed congestion, but was otherwise normal in appearance.

The Gasserian Ganglia. Right: The veins near the ganglion were engorged with blood. The ganglion was of ordinary size. On the upper surface, just below the entrance of the sensory root and between and about the exit of the ophthalmic and superior maxillary branches, the veins were congested and stood out prominently. The same appearance was seen on the posterior surface, but the congestion was less marked. Left: The vessels about the ganglion were engorged, as were the veins about and between the origin of the ophthalmic and superior maxillary branches of the ganglion. About the root of the superior maxillary branch this was very marked, and there was also hemorrhage into the capsule at this part on the posterior aspect of the ganglion. The fifth nerve and the branches from both ganglia appeared normal. The cord and the posterior root ganglia were not removed.

Chest: The chest was well formed; the sternum, ribs, and costal cartilages were normal.

The right lung was bound down by old but thin adhesions; the pleural cavity was obliterated. The right lung was consolidated throughout. On section it was firm and airless, of a grayish color, and quite granular in appearance. The mucosa of the bronchi was congested, otherwise normal.

The left pleural cavity contained about 100 c.c. of seropurulent fluid. The surface of the lower lobe was covered with a thin fibrinous exudate. The lung crepitated throughout. On section the lung was markedly congested and edematous, but was free from consolidation.

The description of the other organs is without present interest, and will therefore be omitted.

Cover-slips from the right lung and left pleura showed encapsulated lanceolate diplococci.

Plate cultures from both lungs, the left pleura, and heart's blood and pericardium showed pneumococcus in pure culture. Similar cultures from the liver, spleen, kidneys, and gall-bladder remained sterile.

Histologic Examination. Lungs: Sections of the consolidated area showed well-marked croupous pneumonia, with lanceolate diplococci in the exudate. Sections of the other organs, with the exception of the skin of the lip and nose and of the Gasserian ganglia, showed nothing of present illness.

Skin of Lip and Nose: Bits of tissue were cut out and hardened in formalin and 95 per cent. alcohol, and sections were stained in carbol-toluidin blue and eosin, hematoxylin and eosin, and by Weigert's fibrin method.

The changes found were practically identical with those from the herpetic areas of Case I.

As in Case I., few well-developed vesicles remained, the surface of the lesions as a rule being covered with a crust of amorphous and fibrillated fibrin and fibrinoid material, containing desquamated and often necrotic epithelial cells, polymorphonuclear and mononuclear leukocytes and cellular and nuclear fragments. Here and there rather small vesicles were to be made out. As in Case I. some were elongated cavities in the exudate or in the superficial layer of the skin just beneath the horny layer; while others were between the underlying inflamed papillæ and the epidermis. Most of the latter cavities were small, and their walls were formed of necrotic epithelium and their floors of the naked papilla. In some places ballooning of the cells of the epidermis could be made out. In many places the margin between the necrotic and the unchanged epidermis was rather clear cut, but in some places near the necrotic portions the small vesicles could be made out in the neighboring otherwise normal epidermis. In most places at the site of the lesion the whole thickness of the epidermis was necrotic. Beneath the fibrinous layer there were, in all sections examined, changes in the epithelium, marked coagulation and liquefactive necrosis, and hyaline transformation of the cells. The papillary layer and outer part of the corium were similarly affected. There was in many places marked nuclear fragmentation. The epithelium of the sweat glands and some of the hair follicles, when present, showed changes—swelling and liquefaction and often a reticular appearance. Some cells were markedly swollen; many showed coagulation necrosis; many nuclear fragments were to be seen. The bloodvessels, especially the capillaries and small veins of the papillæ and corium, were markedly dilated. Some were crowded with leukocytes. In some of the superficial vessels there were thrombi composed of pink staining material.

The papillæ and the superficial portions of the corium were diffusely infiltrated with great numbers of polymorphonuclear neutrophilic and large and small mononuclear leukocytes and some plasma cells. The leukocytic infiltration could also be traced along some of the small vessels into the deeper layers of the corium. About some of the superficial veins and capillaries often large numbers of red blood cells had escaped into the tissue. Some of the lymph spaces were dilated.

The lesions here, as in the herpes of Case I., were both degenerative and exudative, and involved both epidermis and corium. No inflammatory changes were found in nerves in the skin. No bacteria were found in the lesions of the skin, but in the superficial part of the fibrinous exudate in sections taken from the vestibule of the nose, diplococci, and some bacilli, morphologically like B. mucosus capsulatus, were found.

Gasserian Ganglia: The ganglia with the fifth nerve roots and the origins of the ganglionic branches were hardened in formalin (10 per cent. solution).

The two ganglia were mounted in celloidin side by side on the same block and cut in serial sections, every other section being stained and mounted in order. Many of the alternate sections were also stained.

In mounting on the block the left ganglion was at a somewhat higher level than the right; so in the parallel sections as mounted for histologic study the two ganglia were not identical in structure, but as the series was followed to the end the right ganglion was found to be similar to the left in structural detail.

Left Gasserian Ganglion: In Sections 1 to 8 there were no ganglion cells near the superior maxillary branch. The veins about this branch were enormously dilated and filled with red blood cells. In some places in the largest vein there were collections of leukocytes and larger and smaller granular masses, suggesting fibrin. No changes were found in the opposite end of the ganglion. About the dilated veins there was hemorrhage into the pia or capsule of the ganglion. In Section 9 a small oval bit of ganglion tissue containing ganglion cells became apparent near the superior maxillary branch. In Sections 9, 10, 11, and 12, corresponding to this, there was capsular and subcapsular hemorrhage with compression of the superficial ganglion cells. In Sections 15 to 35 the small strip of ganglion tissue in relation with the superior maxillary branch became very much larger and formed an elongated strip of tissue, traversing the thin portion of the ganglion, reaching from the side of the superior maxillary branch to, but not uniting with, the larger ganglion mass corresponding to the origin of the inferior or third branch. About the middle of this strip there was marked congestion of the veins about the superior maxillary branch into and here and there just beneath the capsule of the ganglion. This congestion and hemorrhage must have compressed the ganglion cells in this region. Sections 36 and 37 showed the first well-marked changes in ganglion cells and interstitial tissue. About the central portion of this strip of ganglion tissue some of the ganglion cells were vacuolated; others were very pale, non-granular, homogeneous, and stained poorly. The nuclei showed no special changes. Some ganglion

cells were evidently necrotic, the cytoplasm staining diffusely and the nuclei being displaced to one side. Here, especially about the changed ganglion cells, there was marked cellular infiltration, with plasma cells, lymphocytes, and polymorphonuclear neutrophiles.

These cells were both in the interstitial tissue and grouped about changed ganglion cells, which were evidently compressed thereby. In places there had evidently been a proliferation of the endothelial cells about the ganglion cells.

In Sections 40 to 60 the congestion and hemorrhage were not noticeable, the cellular infiltration being inconspicuous.

Beginning in Section 73, cellular infiltration became marked again. In Section 77, in the above mentioned strip of ganglion tissue, involving an area of from twenty to twenty-five ganglion cells, there was marked cellular infiltration with interstitial hemorrhage. Some of the ganglion cells were necrotic. Smaller areas of interstitial cellular infiltration were found near this area.

Section 78 showed at the border of the same hemorrhagic area a group of degenerated ganglion cells surrounded by large numbers of lymphocytes, plasma cells, and polymorphonuclear leukocytes, red blood cells, and proliferated endothelial cells of the pericellular spaces. The ganglion cells of the affected area showed the same changes described above; many had entirely disappeared. They seem to have been compressed and destroyed by the interstitial exudate and hemorrhage. A few ganglion cells in this area were the seat of large vacuoles. Nuclear figures could be made out here and there in the cells of the interstitial infiltration. In most of the sections from 60 to 85 these changes were more or less well marked. The areas of hemorrhage could be traced in them all. The changes in the left ganglion were lost after the 95th section.

Right Gasserian Ganglion: All the sections showed congestion of the veins and capillaries about the second or superior maxillary branch, as described for the right ganglion. Hemorrhage was, however, absent. In Sections 80 to 95 a few areas of cellular infiltration were found in the area corresponding to that showing similar changes in the left ganglion. These areas of cellular infiltration were small and scattered, and nothing like so well marked as those found in the left ganglion. In both ganglia a considerable number of amylaceous and hyaloid bodies were found in the lymph spaces.

In preparations of the fifth nerve and of the superior maxillary branches of both sides, made by Marchi's method, no degenerations were to be found.

No bacteria were found in the ganglia or in the dilated veins.

That herpes zoster following some part of the distribution of the trigeminal nerve is due to changes in the Gasserian ganglion is supported by observations on four previous cases.

Wys, in 1871 (quoted by Head and Carpenter), reported a case of herpes zoster involving the distribution of the whole of the first divi-

sion of the trigeminal nerve; the patient died on the seventh day of the eruption. There were thrombosis of the opthalmic vein, abscesses of the eye muscles and purulent infiltration of the connective tissue of the eyeball. There was hemorrhage about the origin of the ophthalmic division and about the inner side of the ganglion. Microscopically there was extravasation of blood into the ganglion and into the first division of the nerve, with purulent inflammation of the ganglion.

Sattler, in 1875 (quoted by Head and Carpenter), reported a case of herpes ophthalmicus of the right side in a man of eighty-five, occurring some days after carbonic oxide gas poisoning. Death occurred fourteen days afterward. In the corresponding Gasserian ganglion there was destruction of ganglion cells and small cell infiltration. The ophthalmic branch of the nerve showed degeneration, the other branches being normal.

Head and Carpenter reported a case of herpes of the right frontal region, in which 190 days later, at autopsy, they found hemorrhage and destruction of ganglion cells in the right Gasserian ganglion.

In another case these authors studied the right Gasserian ganglion thirty days after an attack of herpes of the chin and cheek of the right side of the face (third division). "In that portion of the right ganglion which receives the fibres of the inferior maxillary branch of the nerve" there was congestion of the bloodvessels, destruction of ganglion cells, and cellular infiltration. Degenerated fibres were found in the fifth nerve central to the ganglion, in the pons and medulla, as well as in the inferior maxillary division of the fifth nerve.

Both of the last two cases were subjects of general paralysis. Wys' case was apparently spontaneous, while that of Sattler followed carbonic oxide gas poisoning. As far as I am able to find, these comprise all the observations on the relation between changes in the Gasserian ganglia and herpes distributed along the course of the trigeminus. Of these four cases, three were examples of ophthalmic herpes and one of inferior maxillary herpes. I am not aware that the relation of the changes in the Gasserian ganglia to herpes of the upper lip and nose, occurring either spontaneously or in the course of pneumonia, malaria, cerebrospinal meningitis, gastrointestinal disorders and other infections and intoxications, has been investigated.

I wish to call attention to the identity of both the lesions of the skin, and in the nervous system of these two cases of herpes,

the one of the trunk and the other of the upper lip and nose, both occurring during the course of acute croupous pneumonia. Reference to the detailed descriptions will, I think, show that the lesions agree in all important particulars and only differ in severity. The extent and severity of the skin lesions are also in definite relation to those of the corresponding ganglia. The skin and ganglion changes of Case II. (trigeminal distribution) were more severe than in Case I. (dorsal, 11).

One is forced to the conclusion that the herpes of the trunk and the herpes of the lip and nose occurring in these two cases are identical clinically, histologically, and probably etiologically. They further demonstrate that the ganglionic lesions of herpes zoster of the trunk and herpes of the lip and nose occurring in pneumonia are identical with those described by previous observers, for herpes zoster of the trunk and extremities, and herpes distributed along both the first and third divisions of the trigeminus, occurring both spontaneously (idiopathic herpes) and secondarily to acute infections, as cystitis, bronchitis, and acute tubercular pneumonia (Head and Carpenter), after poisons as carbonic oxide gas (Sattler), and the invasion of tumors (Head and Carpenter). As far as I have been able to learn, no anatomic studies have been made on the lesions of the nervous system in herpes of the lip and nose occurring in malaria and other continued fevers, in pneumonia, cerebrospinal meningitis, coryza, or gastrointestinal disorders. We are also without similar observations in genital herpes. .In the case of the latter, however, Unna's description of the skin lesions based on observations in three cases, is apparently identical with his findings in a case of herpes labialis in an individual dead of a continued fever, with these lesions of our cases and with those found by Head and Carpenter and others on herpes zoster. Unna, however, found marked ballooning of the epithelial cells of herpes zoster (trunk?) a condition not found by him in herpes genitalis and his one case of herpes labialis. In our case of labial and nasal herpes, in some places the swelling and liquefaction of the epithelial cells, especially in the hair follicles, was better marked than in the case of herpes of the trunk. It seems likely that in a necrotic and exudative process passing rapidly through different stages the changes would not be uniform in the lesions of each and every case. All that can be said at present is that the skin lesions

of our two cases are identical and agree with those described by most authors.

Though there are no previous observations in the relation of changes in the nervous system in herpes labialis et nasalis occurring in pneumonia, and none at all in malaria, for the third acute infectious process in which herpes is common, there are some most interesting and suggestive data. I refer to epidemic cerebrospinal meningitis. In their monograph on this disease, Councilman, Mallory and Wright (*Report of the State Board of Health of Massachusetts*, 1898) call attention to the frequent occurrence of herpes of both the lips and nose, and to the fact that it may appear on other parts of the face and even elsewhere on the body; and in the summary on page 163, they state that "in its (the infectious) extension along the fifth nerve it produces an acute inflammation of the Gasserian ganglion, with destruction and degeneration of the nerve cells composing it." On page 114 they state that sections were made of the Gasserian ganglia in five cases, and of the spinal ganglia in two. The Gasserian ganglia in acute cases were infiltrated with pus and masses of ganglion cells were often separated from their connection. There was more or less hemorrhage; some ganglion cells were small and some devoid of nuclei; some cells contained large vascular spaces. Diplococci were found in some sections. In the more chronic cases the amount of leukocytic infiltration was less, but there was marked proliferation of the interstitial tissue, and in one case there was edema with marked cellular infiltration, especially about ganglion cells, lymphoid, epithelioid and plasma cells being found. There was atrophy, often going into complete necrosis, of the cells (ganglion cells).

The spinal ganglia were not equally affected, but all seemed somewhat swollen and edematous. In microscopic examination much the same changes were found in these as in the Gasserian ganglia. Degenerative changes were, of course, to be found in the nerves. They also showed that these changes may occur rapidly, for purulent infiltration was observed in the ganglia of a goat twelve hours after inoculation of the diplococcus intracellularis meningitidis into the spinal cord.

On page 125 they state that "in one case the herpetic vesicles on the lip were examined. In them there was extensive infiltration, with pus cells in the tissue around the vessels, with proliferation of

the fixed cells of the tissue." No mention is made of the epithelium; no diplococci were found in the pus cells. Unfortunately no statement is made concerning the presence or absence of herpes of either the head or the trunk in the cases showing lesions of the Gasserian and spinal ganglia. In the one case showing skin lesions (small dark, purplish spots on the trunk and extremities) coming to autopsy they found congestion and dilatation of the bloodvessels of the skin with hemorrhage in places, and in some cases proliferation of the cells about the vessels. In the center of the hemorrhagic area there was some infiltration with pus cells, and in one place the upper layers of the epithelium were slightly elevated by the accumulation of pus cells beneath.

These observations furnish at least ample explanation for the occurrence of herpes of both the head and trunk in meningitis. The influence of the changes in the ganglia upon the other changes in the skin are, of course, only conjectural.

Etiology of Herpes. From what has gone before, it is evident that the lesions of the skin and nervous system of primary or idiopathic, or spontaneous herpes zoster of the head, neck, trunk, and extremities are the same, as are also the same lesions in certain cases of herpes of the trunk and face (upper lip and nose) occurring in pneumonia (Howard), and similar lesions of the nervous system in herpes of the trunk occurring in acute cystitis in a man with paraplegia, acute bronchitis, and pernicious anemia in a patient who had taken arsenic, and after the invasion of a lymphosarcoma (Head and Carpenter), and finally in ophthalmic herpes after poisoning with carbonic oxide gas (Sattler).

Primary herpes zoster is regarded by Head and Carpenter and by Van Harlingen (*Amer. Journ. of the Med. Sci.*, January, 1902) and others as an acute specific infectious disease due to an unknown cause having a selective affinity for certain sensory ganglia, in which certain degenerative, destructive, and often inflammatory lesions are produced. These lesions in some unknown way cause acute degenerative, exudative, and proliferative changes in skin, and mucous and possibly serous membranes, corresponding to the nerve distribution of the affected ganglia. There is a considerable amount of evidence in favor of the hypothesis that there is an acute specific infectious process of this nature, but no convincing proof has been so far

adduced in its support. It must be further borne in mind that there is a large group of cases of herpes, either following the action of known toxins (carbonic oxide gas and arsenic), the involvement of ganglia by tumors, or occurring in the course of certain infections, as pneumonia, malaria, and typhoid fevers, and cerebrospinal meningitis (in which as has been shown there are often intense lesions of the sensory ganglia), in all of which the lesions, as far as is known, are identical. Herpes, like pneumonia, meningitis, and inflammation in general, is a pathologic condition, with definite lesions capable, however, of being excited by a variety of causes, and is not always produced by the same causes; an efficient cause being one producing compression, degeneration, or destruction of ganglion tissue. It is not improbable that the primary lesions are often due directly or indirectly to the soluble toxins of various micro-organisms. The special frequency of labial and nasal herpes, and of herpes of the head and face in general in malaria, pneumonia, and cerebrospinal meningitis, is readily explained. In the case of malaria, the organisms in the circulating blood often accumulate in the brain, where the Gasserian ganglia may be readily affected by congestion, the action of toxins, or even by capillary thrombi of parasites. In pneumonia, the organisms or their toxins may locate in the ganglia. What, however, to my mind, seems the most reasonable predisposing cause of the frequent occurrence of labial and nasal herpes in this disease is the marked passive congestion which is so often present. This was especially noticeable in Case II., in which there was marked congestion of not only the bloodvessels and sinuses of the brain and meninges, but of the vessels of and near the Gasserian ganglia themselves, and especially about the second division. This marked congestion, which favors hemorrhage, the action of poisons and organisms in the blood, and thrombosis, may probably of itself, by pressure and by interfering with the nutrition of the ganglion cells, cause degeneration sufficient to excite the herpetic changes.

As Councilman, Mallory and Wright have shown, in epidemic cerebrospinal meningitis, the spinal sensory ganglia, and especially the Gasserian ganglia, are often the seat of extensive changes due to the extension of the infection along nerve sheaths to these ganglia.

There is a priori no reason why changes in these ganglia should not occur in bronchitis and pleurisy. There is also no reason why

peripheral lesion in herpes zoster should not affect the pleura, as suggested by Curtin, just as the same process is known to affect the mouth, cheek, and pharynx. We know nothing in regard to the relation of lesions of the nervous system to the so-called simple herpes (with which labial and nasal herpes of pneumonia, malaria, and epidemic cerebrospinal meningitis have hitherto been included) of the face, especially of the lips and nose, occurring in coryza, gastro-intestinal disorders, and the herpes genitalis. It is to be hoped that observations will be made on this point, and it is not impossible that some cases, at least, will fall in the class we have been considering.

The question Why should the peripheral changes occur after these, the lesions of the nervous system found in herpes? is a difficult one to answer. There is no evidence that the skin lesions are due to the local presence of parasites, infection with which is predisposed by the nerve lesions.

Head and Carpenter are "inclined to think that the trophic disturbances of the skin is an extreme form of activity of the same cells, disturbance of which by afferent impulses along the white ramus produces the hyperalgesia that accompanies visceral referred pain," but they "do not imagine that the eruption of herpes zoster is produced by disturbance of special trophic nerves, but by intense irritation of cells in the ganglion which normally subserve the function of pain, and more particularly that form of pain produced by afferent visceral impulses."

This is, however, far from explaining why irritation of these ganglion cells and nerve fibres causes a severe inflammatory process, marked by intense vascular changes and cell destruction, exudation, and proliferation The presence of hyaline granular and apparently red blood cell thrombi in many of the dilated bloodvessels of the herpetic areas in my cases is of interest, and may account for the hemorrhage, but were hardly extensive enough to explain the necrosis. What was the origin of these thrombi? Were they associated with changes in the vascular endothelium due to nerve changes? Were the hemorrhage and exudation due in part to the increased permeability of the vessel walls, the result of loss of nerve control or nerve irritability? These are some of the questions awaiting solution.

CONCLUSIONS. 1. Herpes zoster is a pathologic process, like pneumonia for instance, with definite lesions of certain sensory ganglia,

sensory nerves and the skin, capable of being excited by a variety of causes. It is probable that the primary ganglionic lesions are commonly due, directly or indirectly, to the soluble toxins of various micro-organisms. The skin lesions may be on the head, neck, trunk, or extremities, corresponding to the Gasserian and posterior root ganglia affected.

2. Various forms can be distinguished: (*a*) Spontaneous or primary herpes, thought by Head and Carpenter and others to be a specific infectious disease, the specific causal agent of which has a special affinity for sensory ganglia (posterior spinal and Gasserian). (*b*) Herpes occurring after certain definite toxic agents, as arsenic and carbonic oxide gas, etc. (*c*) Herpes occurring in the course of certain acute infectious diseases, as pneumonia, cerebrospinal meningitis, and probably of malarial and typhoid fevers. The lesions of the ganglia and of the skin in the above three forms are the same, the processes therefore presumably identical. (*d*) Herpes simplex, so-called, affecting the lips and nose in coryza, gastrointestinal intoxication, etc., and genitals (herpes genitalis) has not been sufficiently investigated to be classified; no evidence exists for or against its connection with changes in the nervous system.

3. As far as the changes in the skin in herpes are concerned they are illustrations of particular forms of necrosis and inflammatory reaction, and as in similar lesions in other organs, can probably be excited in a variety of ways.

4. Herpes should be classified according to its relation to changes in the nervous system, and to this end every possible opportunity should be embraced for extending our knowledge in this direction.

DISCUSSION.

DR. THOMSON: We know that a great many years ago the appearance of herpes after croupous pneumonia was considered a favorable sign, and I must say my own impressions are strongly in favor of that view; clinically, it appears to me to have been a symptom of favorable import. I recommended to my house staff in a case of severe pneumonia last spring in which herpes appeared, that they should examine the fluid itself to determine whether there was any difference between it and other herpes. It was done, but no difference was made out. The patient went through the disease, however, and, though it was a very severe attack, came out all right.

PRELIMINARY REPORT ON A STUDY OF SMALLPOX.

By JAMES EWING, M.D.,
OF NEW YORK CITY.

During the past year I have studied from autopsies at North Brother Island, New York City, twenty-nine cases of smallpox. Access to this material was obtained through the kindness of Dr. H. M. Biggs, Dr. W. H. Park, and Commissioner Cosby, of the New York Department of Health, and to these gentlemen I desire to express my great obligation, as well as to Drs. Ray and Berry, resident physicians at the Island.

The general plan followed in undertaking the study of a disease with which I was entirely unfamiliar was the following:

1. The pathologic anatomy.
2. The histology.
3. The routine bacteriologic study of the heart's blood and cutaneous lesions by ordinary methods.
4. The same field treated by special methods of bacteriologic study.
5. Experimental variola.

In the first three of these departments the work has been nearly completed, while in the last two only a beginning has been made.

I. Pathologic anatomy.

The Cutaneous Lesions. One may divide these lesions into the following classes:

1. Primary hemorrhagic smallpox, fatal on the second and third days, before the development of general discrete variolous lesions, and marked by diffuse hemorrhages into the skin and mucous membranes. This is the most severe type of the disease, and its violence is most appalling. The series include three such cases.

2. Secondary hemorrhagic smallpox. (Eight cases.)

Here the usual variolous lesion is early complicated by hemorrhages into the skin and mucous membranes, and sometimes these hemor-

rhages are so early and diffuse as to constitute a transitional variety between primary and secondary hemorrhagic smallpox.

In addition to the usual type of this variety, in which the hemorrhages occur early in the disease, one hemorrhagic case was encountered in a "bleeder," in which the early pustules became filled with blood, and a general punctate hemorrhagic eruption appeared on the sixth day. Also on the ninth day of another case the usual well-filled pustules suddenly became the seat of a distinctly secondary hemorrhage, producing a true "black smallpox."

3. Confluent or conglomerate smallpox. (Nine cases.)

This is the most common type of the disease, and is often fatal.

4. Discrete smallpox. (Seven cases.)

This type of the disease is usually benign, but a good many cases die from complications.

5. In a newborn infant dying at fourteen days the eruption consisted of about a dozen large blebs scattered over the trunk.

Two interesting variations of the usual cutaneous lesions were observed. While various stages of the eruption are often to be found in the same cadavers, in one case were exhibited two distinct crops, one consisting of large hemorrhagic pustules, the other appearing several days later as very numerous small vesicles. In another case a scanty discrete scabbing lesion was complicated in convalescence by a diffuse scarlatina-form eruption. Possibly this was scarlatina grafted on variola, but no further cases developed in this children's ward, and in another such case there was in due time a typical scarlatinal desquamation.

Respiratory Mucous Membranes. I examined the upper nares in a few cases, but was disappointed in the extent of the process found, which was distinctly less than in the pharynx, although variolous ulcers and diphtheritic membrane were encountered. The posterior nares, fauces, and pharynx usually showed a profuse eruption ulcerating early and frequently becoming diffuse and diphtheritic.

The trachea usually presented the most severe lesion in the cadaver. In eighteen, or practically all of the acute cases, there was a diffuse diphtheritic lesion extending from the epiglottis to the finest bronchioles. In the primary hemorrhagic cases there was diffuse hemorrhage and very superficial diffuse necrosis. If not fatal, this lesion, or a milder one, is succeeded or replaced by a catarrhal or

purulent bronchitis, as found in five cases dying late in the disease. In three cases with mild discrete cutaneous lesions the trachea showed discrete pustules. In one remarkable case the trachea exhibited very numerous early lesions of pure conglomerate variola. Twice the respiratory mucosa showed a severe and active process when the lesion in the skin was scanty and nearly healed. One diphtheritic case failed to survive tracheotomy on account of extensive edema of the trachea and neck compressing the air passages.

The conclusion was reached that the lesion of the respiratory mucous membrane is, as a rule, earlier than that of the skin, and far more important in causing death.

Lungs. Seven cases failed to show any consolidation in the lungs. They died late in the disease, without much involvement of the trachea. Two cases showed a late lobar pneumonia. All the others exhibited some grade of lobular pneumonia, which was usually the chief immediate cause of death. The intensely black, congested, edematous lungs of the hemorrhagic type of the disease are practically pathognomonic. A fibrinous pleurisy was occasionally seen.

Heart. Three cases showed acute ulcerative endocarditis. One developed this lesion from the first, and died on the eighth day. One developed the lesion as the skin was healing, and one was convalescing and out of bed before the cardiac symptoms were detected.

Liver. Various grades, usually marked, of acute degeneration were regularly noted.

Kidneys. Acute degeneration was the usual lesion. Once acute exudative and productive nephritis was found. In three primary hemorrhagic cases there were some minute hemorrhages throughout the organ. In the pelvic epithelium I found no specific variolous lesions, but failed to look for them with unusual care. In the primary hemorrhagic cases the pelvis showed diffuse hemorrhagic and diphtheritic inflammation. The urine in these cases was very bloody.

Aside from petechiæ I found no lesions in the bladder.

The Gastrointestinal Tract. Several cases showed numerous variolous ulcers of the epithelium of the esophagus. In the primary hemorrhagic cases there was more or less diffuse diphtheritic process in the esophagus. In five cases there were numerous minute variolous ulcers in the stomach, and once there were large areas of diphtheritic necrosis. Petechiæ were common. In one confluent hemor-

rhagic case there was marked hemorrhage from the intestines and a diphtheritic enterocolitis, affecting the entire colon and lower ileum. In the primary hemorrhagic cases the stomach and entire colon, but not the small intestine, showed diffuse infiltration of the mucosa with disintegrating blood.

Lymphatic System. Extreme congestion and swelling of the nodes was a constant gross sign. The swelling of the mesenteric and gastro-intestinal lymphatic structures was very marked and in proportion to the intensity of the disease. The spleen was large, firm in the early stages, drained of lymphocytes and flabby in the late stages, sometimes exhibited hemorrhages and focal necroses, and often a peculiar mottled condition which I have not encountered in other diseases.

The marrow showed the same variations in its cellular contents, and was more often the seat of hemorrhages.

Testis. I found three cases of acute necrotic inflammation of the testis, and it may have been more common, as the testes were not always examined even in the gross. In one confluent case the urethral epithelium was untouched. In seven females I found no specific lesions in the uterus or vagina.

Eye. There were conjunctival and bulbar hemorrhages in the primary hemorrhagic cases. No variolous lesions were to be seen in the conjunctival epithelium. In some cases they might have escaped observation.

The middle ear looked normal in two cases.

Brain. The brain and meninges were congested and œdematous when examined, but were not touched in the primary hemorrhagic cases.

II. Histology. The histologic examination of the tissues in these cases has led to the conclusion, stated by Weigert many years ago, that the first effect of the variolous process in ordinary intensity is coagulation necrosis, followed by liquefaction and exudative phenomena. In the epithelial tissues the lesion shows a marked focal character, often becoming diffuse. In some other tissues, especially in the spleen, marrow, and testicle, the lesions are apt to be focal. In the lungs the focal lesions develop by extension down the air passages. In other tissues the lesions are those of a diffusible toxin. The hydropic changes so prominent in the cutaneous vesicle seem to be secondary to coagulation necrosis, and to result from exudation into the necrotic

area. This conclusion is not in accord with my preconceived notion that the virus of smallpox must be one which primarily liquefies tissues.

Another prominent histologic character is the extreme congestion attending the local process. I have never seen anything else approaching the remarkable distention of all the vessels of the respiratory submucosa of an ordinary case of smallpox. This same congestion about cutaneous lesions causes the frequent hemorrhagic character of the eruption. In the primary hemorrhagic cases all the cutaneous and mucous surfaces are literally drenched with blood.

A third main histologic character is the exclusive preference of the lesion for epithelial tissues, which seems to indicate that the virus requires epithelial albumin for its propagation.

Only the bladder and small intestine, possibly also the uterus and vagina, seem to escape involvement. On the other hand, the parenchyma of organs, as the spleen and the testicle, may show a somewhat specific localized process.

The Blood. The blood was examined in twelve cases, with results similar to those reported in the recent elaborate study of Courmont and Montagard (*Journ. de Phys. et de Path. gén.*, 1900, pp. 557, 781). The presence of from 30 to 50 per cent. of large and medium sized mononuclear cells and some myelocytes, with distinct leukocytosis and active fever, is a rather pathognomonic sign of the disease. It is worth while pointing out that the high proportion of mononuclear cells is frequent at a period when the cutaneous exudate is highly purulent and when the pustules commonly yield cultures of streptococcus pyogenes.

In the primary hemorrhagic cases there is during life beginning dissolution of the red cells, with hemoglobinemia, and after death the dissolution continues, so that in sections of tissues there may be abundant deposits of pigment similar to those seen in puerperal septicemia of streptococcus origin.

I had hoped that the examination of both the blood and tissues by Nocht's method, which seems especially adapted to the demonstration of protozoa, might yield some interesting information. The results obtained by a laborious study of all the cases by this method were entirely negative, as I found no traces of protozoa.

III. Bacteriologic. The plan of the study included the bacteriologic examination of the heart's blood and cutaneous lesions: first, by the

ordinary methods, and, later, by any special methods which the previous study might suggest.

a. Systematic examination of smears of the cutaneous lesions in all stages, stained by various methods, led to the following conclusions:

1. Vaccine bodies are present in all stages of the specific lesions, and their numbers are proportional to the hemorrhagic character of the lesion.

2. Streptococci are present in all the specific lesions at a very early stage, frequently in enormous numbers, but very often scantily, and sometimes cannot be detected in the smears of vesicles and even of pustules.

3. The next most common bacterial form encountered in smears is a fine bacillus resembling in general a minute Klebs-Loeffler. It corresponds to the bacillus described by Klein and Nakanishi in vaccine. It is discussed later.

4. Smears of variolous lesions always contain a great variety of minute bodies resembling bacteria, cocci, or bacilli, which cannot be positively identified as bacteria, but which open up wide possibilities for the demonstration of a bacterial origin of the disease.

b. Cultures upon blood serum and other media were made in all cases from the heart's blood, and usually from several vesicles in the skin.

A streptococcus was obtained from the heart's blood in all of the twenty-nine cases. Twice it was associated with Klebs-Loeffler in cases showing diffuse diphtheria of the pharynx and larynx, and in two cases, both dying late in the disease, with much ulceration of the skin, staphylococcus aureus also grew.

The abundance of the growth of streptococcus in the heart's blood was directly proportional to the severity of the disease, and was also influenced to a less extent by the time intervening between death and the postmortem.

It was least abundant in cultures taken after death in cases dying in the early stages of the eruption, and in such cases, to ensure a successful culture, at least ½ to 1 c.c. of blood should be planted.

After death it multiplies rapidly in the body. In hemorrhagic cases it is more abundant, and in three primary hemorrhagic cases a score of chains of streptococci were found in each oil-immersion field of the thinly spread heart's blood four to six hours after death, while

the cultures were extremely profuse. It was also very abundant in the blood smears of a newborn infant dying on the fourteenth day, with very scanty bullous eruption.

I made five examinations of 10 c.c. of blood taken from the basilic vein during life. They were all sterile. Arnaud (*Rev. de Méd.*, 1900, p. 303), however, found streptococci in the circulating blood in two primary hemorrhagic cases. Only one of my five cases died, and it was not of the primary hemorrhagic type.

Cultures of the skin were made in twenty-three cases. The skin was first pencilled with 5 per cent. formalin for two minutes, then in sterile water, and the cover of the vesicle removed with sterile instruments. A platinum needle was then touched to the base of the lesion and the material transferred to blood serum, etc.

In seventeen cases streptococci grew alone, once with staphylococcus aureus, once with a fine bacillus (Bac. 19), once staphylococcus aureus only was obtained, and three cases gave no growth. In one of the sterile cases streptococci were afterward found in sections of the skin. In several cases other bacteria grew in isolated colonies, which were set aside as contaminations.

Seeing that the streptococcus was found by this crude technic in nearly 90 per cent. of the cases, I feel justified in concluding that it is invariably present in the cutaneous lesions as well as in the heart's blood. If the skin be allowed to remain at room temperature for twenty-four hours I believe the streptococcus can always be isolated from it by culture, which, of course, would not prove it present there during life.

The streptococcus showed many peculiarities, all of which may characterize this micro-organism as obtained from other sources. It grew best on blood serum, feebly or luxuriantly; it sometimes clouded the broth in initial, but never in subcultures; its chains were very short, except in ascitic broth, in which the chains were very long. The individuals varied from an extremely minute size to 3 to 4 μ in diameter. It sometimes grew in bacillary form, as described by Hektoen, from diphtheria, and sometimes it split lengthwise instead of sidewise. Under the skin of mice it once killed in four hours. When rubbed into the shaved ear of a rabbit it killed in forty-eight hours with general septicemia. Sometimes it was less virulent for rabbits.

Inoculations. Material from smallpox pustules was inoculated into rabbits, into the conjunctiva, skin, and veins; into guinea-pigs by the same routes; into rats subcutaneously, and into two monkeys by vaccination. The monkeys—one a *rhoesus* and the other a large African black-faced fellow—both yielded a rather typical form of inoculated variola with discrete pustules, the scab dropping after two weeks. All other experiments were negative.

The streptococcus was inoculated repeatedly into rabbits, pigs, rats, one calf, and two monkeys. It sometimes killed the small animals, but never produced anything like variolous lesions in any of them.

Bacillus 19 was a minute bacillus obtained from the skin of Case 19, and once later from the heart's blood. It sometimes exhibited cross striations like a minute Klebs-Loeffler. After remaining inoculated in a calf two weeks it appeared in smears of pus as a minute coccus, but regained its bacillary form on first cultivation. It grew as an almost transparent film on agar and blood serum, and its chief character was the active fluidification of blood serum and gelatin. It reminded one so strongly of the bacillus isolated by Martin from vaccine, and claimed by him to be the specific contagium of cowpox, that I gave it considerable attention.

It killed a rabbit in forty-eight hours with septicemia when rubbed into a scarified area of the skin. A calf kindly placed at my disposal by Dr. Park was vaccinated, with a negative result. It was then injected beneath the skin of this calf, producing an abscess containing the germ as a coccus, pure; and the first attempt to produce vaccinia in this calf failed, but a second extensive vaccination gave a "dry take." On three monkeys it had no effect whatever. Smallpox blood serum agglutinated the bacillus but feebly. This bacillus was finally inoculated, together with streptococcus, in a calf and a monkey, always without specific lesion.

From vaccine and from the skin of a case of variola I obtained Nakanishi's bac. variabilis, which gave negative results when vaccinated on calves, monkeys, and small animals.

Lastly, I have inoculated the streptococcus with the macerated skin of smallpox sterilized by heating to 75° C. for one hour on eight consecutive days. This treatment will destroy many but not all ferments, and will leave unaffected many albumoses. The results were negative.

CONCLUSIONS. At the present time, while it hardly seems possible that the streptococcus is the specific contagium of variola, one cannot fail to be strongly impressed by the fact that this micro-organism is present at all stages of the disease and in numbers proportional to its severity.

It is difficult to reconcile the principles governing secondary infection by streptococcus with the presence of this bacterium in the blood during life, and with its enormous numbers in the blood very shortly after death of the primary hemorrhagic cases. In these cases it cannot be doubted that the streptococcus completely overshadows any other bacterial agent that may be present, and the idea of a secondary infection in such cases does not seem reasonable. I believe that the condition in these cases should be regarded rather as a symbiosis of the streptococcus and the specific agent, from a very early period, so early as to be indistinguishable in these cases from a primary invasion.

While not inclined to urge that the streptococcus is the specific agent in variola, I believe it will always remain impossible to reproduce the disease, especially in its fulminant types, without the aid of this micro-organism.

A PRACTICAL METHOD FOR DIFFERENTIATING BETWEEN VARIOLA AND VARICELLA BY MEANS OF THE INOCULATION OF MONKEYS.

By WILLIAM H. PARK, M.D.,
OF NEW YORK CITY.

THE cutaneous inoculations of a number of monkeys with the contents of the vesicles and pustules of smallpox patients during some studies on the etiology of smallpox resulted in such characteristic lesions that it occurred to me that through inoculations of the monkey we might have a reliable means of differentiating doubtful cases of variola from varicella.

Altogether twelve monkeys have been inoculated with virus collected from eighteen cases of smallpox. The first six monkeys were inoculated with a single fresh smallpox virus gathered from typical cases of smallpox in the late vesicular or early pustular stages. The pustules or vesicles were scraped with sterile ivory points, and the contents inoculated upon the abraded skin of the abdomen of the monkey in a way similar to that carried out in ordinary vaccinations of persons with vaccine virus. Java monkeys were chiefly used. In every case upon the second day the area inoculated was slightly swollen. The central part of this area developed on the third or fourth day into a more or less typical vesicle, later changing into a pustule. The skin at the margin of the vaccination was at this time infiltrated. The vaccination ran its course in from eight to twenty days, leaving a scar. Three monkeys were then inoculated with virus in two separate spots, gathered from six cases of typical smallpox; but here the virus was allowed to dry for five days before being used. In every insertion a successful vaccination resulted. In six further cases of smallpox an ivory point was simply carried through the vesicle, getting in this way a small drop of the fluid on the point.

Three monkeys were inoculated with these six ivory points, and five of the six insertions caused successful vaccinations.

The conclusion reached from these experiments was that some varieties of monkeys are very susceptible at the point of inoculation to smallpox virus, and if the base of one or more vesicles or pustules was well scraped, sufficient virus would probably, and, perhaps, surely, be obtained to inoculate successfully a suitable monkey. Simply puncturing a vesicle did not give sufficient active virus to ensure regularly a successful vaccination. Further, that five days' drying, and probably a much longer period, would not destroy the activity of the virus. With varicella the results were very different. Six cases of typical varicella were selected, and vesicles from these scraped, and two monkeys inoculated. In none of the insertions was there any reaction at all similar to that obtained from the smallpox virus.

At the end of twenty-four hours the abraded surfaces in half the insertions were practically normal in appearance. In several a slight redness persisted for two or three days, but there was no development at all of vesicles or pustules. These experiments, in which the insertion of smallpox virus in the skin of the monkey resulted successfully seventeen out of eighteen times, and the absence of all signs of a successful vaccination when the material from varicella was taken, seem to me to give us the basis of a reliable test to separate doubtful cases into either those of smallpox or chicken-pox. All who have been brought in contact with these two diseases where there is no clear previous history know that there are from time to time examples of both that almost defy a positive diagnosis. It is true that in the inoculation of the cornea of a rabbit with the virus of these two diseases we have in the production or absence of production of the vaccine bodies a fairly reliable test. To carry out this, however, requires considerable skill in inoculating the eyes of the rabbit and a trained pathologist to examine the specimens for the presence of the vaccine bodies.

During the past four weeks three cases have occurred in New York City in which the diagnosticians of the Department of Health differed or were in doubt, and the monkey inoculation was at once tried. The first case was a child, aged two and a half years, where there was a very general crop of vesicles and pustules. The disease ended fatally through a complicating bronchopneumonia. The day before death the child developed laryngeal stenosis, with signs of bronchopneu-

monia. Neither diphtheria bacilli nor the lesions of diphtheria were present. Several illy-developed vesicles were present on the mucous membranes.

Two men trained in the study of variola considered the child to have smallpox; two others equally trained considered that the child had chicken-pox. The monkey very thoroughly inoculated showed no reaction whatever. Later, a number of severe and several fatal cases of chicken-pox developed in the institution from which the child came.

The second case was that of a young adult who had a large number of vesicles, changing to pustules, on the face and trunk and limbs. There were a very few on the palms of the hands. There were no vesicles on the mucous membranes. This man was considered to have chicken-pox, but the diagnosticians were not certain, and the case was held for observation.

The third case was one similar to the previous one, except that there were a number of vesicles and pustules on the face which appeared like smallpox. The monkeys inoculated from these two cases showed no reaction. In both these latter cases the lesions rapidly dried up. In the last one, however, some pigmentation at the site of the pustules was left, which is unusual in chicken-pox.

A number of varieties of monkeys were tested, with very similar results. The Java monkeys were the best for this purpose.

CONCLUSIONS. 1. That virus obtained from scraping developed vesicles or pustules of smallpox when inoculated into the skin of the monkey in the manner in which human vaccination is performed, causes within forty-eight hours a local infection similar to a moderately severe vaccination with cowpox.

2. Virus from well-developed vesicles and pustules in cases of chicken-pox does not infect monkeys.

3. The inoculation of monkeys affords us a means, in doubtful cases, of differentiating between smallpox and chicken-pox within a period of three days.

4. A single positive inoculation is sufficient to establish a diagnosis of smallpox.

5. A negative result in one animal should be confirmed by a second animal before establishing a diagnosis of chicken-pox, since it is possible that just as vaccination at times fails in men variolation may fail in monkeys.

NEGATIVE RESULTS OF ATTEMPTS TO CAUSE THE ACTIVE PRINCIPLES OF VACCINE AND SMALL-POX VIRUS TO PASS THROUGH FILTERS IMPERVIOUS TO BACTERIA.

As is well known, attempts to produce vaccination with the filtrate of vaccine virus which had passed through a Chamberland or Berkefeld filter have uniformly failed when the experiments were properly carried out.

It is of so much importance to be certain that the vaccine organisms cannot pass the filter that it was thought worth while to test the matter in a somewhat novel way. The present experiments were undertaken with the idea of using crushed virus and a concentrated filtrate.

It was thought conceivable that the vaccine organisms might be small enough to pass through the filter, and still, because of being contained in the epithelial cells, they might not pass, the cells themselves being kept back. It was also thought possible that the filtrate might contain a few vaccine organisms, and yet have an insufficient number to cause a successful vaccination. It seemed worth while, therefore, to quickly evaporate the filtrate and try to produce vaccination with this. The following experiments were tried:

Fresh vaccine virus was dried over sulphuric acid in a vacuum. This vaccine material was crushed up with fine sand, using a pressure of twenty-five tons to the square inch. This material was gathered up and recrushed. It was then rubbed with water and separated into two portions. The greater part of one-half was drawn through a Chamberland and a portion of the other through a Berkefeld filter. Both filtrates were evaporated over sulphuric acid in a vacuum.

Calves and rabbits inoculated with the filtrate before and after evaporation failed to show successful vaccination. Control animals were inoculated with the solutions of crushed virus before they had passed the filters in every case, and always produced vaccination. Similar virus was crushed with the sand three and again six times. The filtrate from this material failed to take. Ordinary glycerin-

ated vaccine and active serum from calves were filtered, and failed to take either before or after evaporation.

The results obtained in these experiments indicate that the vaccine organisms failed to pass through the filters not because they were retained in the epithelial cells, but because of their own properties.

Smallpox virus obtained from three fatal cases of smallpox failed after crushing to pass through the filter as determined by inoculating monkeys. All these animals were kept in a special building where no vaccine virus was present.

A most instructive accident happened during the earlier part of this investigation. Three calves were inoculated with the vaccine filtrate, and put in the vaccine building in the same room with two regularly vaccinated calves. All the filtrate calves developed several typical vaccine vesicles. Four other calves were then shaved on their bellies and on the inner surface of their thighs. They were all incised as for vaccination, but no vaccine was rubbed in. Three of the four developed a number of typical vesicles. This experiment seems to me to indicate the uselessness of trying experiments with vaccine or smallpox virus in rooms which hold calves producing virus.

Once the vaccine was crushed with sand six different times. At the end it was practically free from living bacteria but was still active as vaccine. Further crushings destroyed the vaccine virus also. For the supply of the large quantity of vaccine virus used in these experiments I am indebted to Dr. J. H. Huddleston, who directs the vaccine laboratory of the Department of Health of New York City.

A CLINICAL STUDY OF 135 CASES OF EMPYEMA BASED UPON THE BACTERIOLOGIC FINDINGS IN THE EXUDATE.

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A CONSIDERABLE number of writers have examined the relation of empyema to various specific bacteria, and the present paper is an attempt to throw further light upon some of the problems which are still unsettled.

It may be useful at the outset to review hastily some of the work done already in this field.

Among the earliest was that of Fränkel (*Charité Annalen*, 1888, p. 147). Serous exudates which become purulent, he agrees, really contained from the first the pus organisms. But though streptococcus and staphylococcus pyogenes are present as admixed infections in lobar and lobular pneumonia, why, he asks, do they appear as exclusive organisms in the empyema thereof?

He classifies his cases as follows:

1. Streptococcus pyogenes and staphylococcus.
2. Pneumococcus; pus thick, adhesive; metapneumonic.
3. Tubercular. T. B., found in only one quarter.
4. Suppuration elsewhere, *e. g.*, retropharyngeal, peritoneal, etc.

Fränkel held that streptococci and staphylococci are not diagnostic. Pneumococcus means metapneumonic infection, and an exudate without organisms is tubercular.

Weichselbaum (*Med. Jahrbücher*, 1886, p. 550), after describing his researches in the bacteriology of pneumonia, says that of eleven cases of primary pleurisy examined, two were empyemata containing streptococci. The autopsy failed to show that a pneumonia had preceded either of them. In a third case, which had followed croupous pneumonia, the pneumococcus was present.

Renvers (*Charité Annalen*, 1889, p. 188) discusses the etiology of empyema, and enumerates the following groups:

1. Metapneumonic empyema containing pneumococci, three cases with good recovery after operation.

2. Complicated metapneumonic empyema, exudate containing pneumococci, staphylococci, and streptococci, three cases; two recovering after operation and one dying. In the latter a gangrenous focus perforated into the pleural cavity; no operation was done.

3. Empyema consequent to suppurative processes of the lungs, especially putrid bronchitis, two cases, both operated upon; one died and one recovered.

4. Empyemas which are septic, result of puerperal fever or other infectious diseases, three cases; two following puerperal fever and one following abscess of the liver. One of these being a bilateral case was treated by aspiration and washing out with boric and creolin solutions, and the other two had the radical operation; all died.

5. A group of four tubercular empyemas, all having the radical operation, with two fatal results; in the other two cases the patients remaining in fair condition, with discharging sinuses.

Netter (*Bull. de la Société médicale des Hôpitaux*, tome vii., p. 441) examined 109 cases of purulent pleurisy with reference to the organisms present, and found the following: pneumococcus, thirty-two times; streptococcus, fifty-one times; saprophytic organisms, fifteen times; tubercle bacillus, twelve times; staphylococcus pyogenes, bacillus capsulatus (Friedländer), twice; M. tetragenus, once; a bacillus like that of typhoid, once; leptothrix buccalis, spirilli, etc.

The staphylococci pyogenes, and especially the aureus, are most common, but they are generally associated with other organisms, usually the streptococci, pneumococci, or tubercle bacillus. Even if none of the latter group was seen with the staphylococci, it was assumed that one of them (the tubercle bacillus, if neither of the others was discovered) was in reality present and was the real cause of the effusion, for staphylococci alone are only exceptionally the cause of serous membrane suppurations.

In six cases no organisms were found. Netter believes that in empyema, as in pus collections elsewhere, the absence of the ordinary pyogenic organisms should suggest tuberculosis.

About 75 per cent. of Netter's cases contained either pneumococcus or the pyogenic microbes, that is: pneumococci were present in 26 per cent.; pneumococci and streptococci were present in 3 per cent.; streptococci were present in 44 per cent.; staphylococci were present in 2 per cent.

In the total of observations which this author collects from Rosenbach, Weichselbaum, Fränkel, and Renvers, the pus organisms also occurred in about three-quarters of the cases, the chief difference being that in this series the streptococcus was found in only 30 per cent., while the staphylococcus pyogenes was present in 14 per cent.

Netter ascribed his streptococcus cases to the following causes: "primary" empyema, fifteen times; grippe (no evident pulmonary disease), seven times; bronchopneumonia, four times; suppurative pneumonia, once; fractured ribs, once; dilated bronchi, once; cancer of lung, once; superficial pulmonary gangrene, twice; quinsy, once; stricture of esophagus, once; cancer of stomach, once; perihepatic abscess, once; otitis media, three times; puerperal infection, six times; scarlet fever, once; an aspirated serous pleurisy, twice.

But a serous fluid may be found to contain streptococci, and would then have become pus, irrespective of any effect of paracentesis. Pneumococcus empyemas were "primary," twenty times; followed pneumonia, ten times; followed bronchopneumonia, once; followed otitis, once.

Probably many of the primary cases were metapneumonic. The putrid pleurisies were almost all sequent to pulmonary gangrene.

Some *tubercular* pleurisies were found in which, even at death, no tuberculosis of the lungs was present.

Pneumococcus empyemata have, according to Netter, a *relative benignity* due to the short life of the organism.

Mortality of empyema of metapneumonic origin equals 2.3 per cent. Mortality of other origin equals 25 per cent.

Pneumococcus organisms are relatively common in children; among twenty-eight cases in children, 53.6 per cent. were pneumococcus; 3 per cent. were pneumococcus and streptococcus; 17 per cent. were streptococcus; 10 per cent. were putrid; 14 per cent. were tubercular.

Thus the relative predominance of pneumococcus and streptococcus is exactly inverted from that observed in seventy-nine adults, where 17 per cent. were pneumococcus and 53 per cent. streptococcus.

Childhood's empyemas, being mostly pneumococcus, are sometimes cured spontaneously, and in general he believes thoracentesis to be sufficient. Streptococcus empyema is graver, and usually demands thoracotomy, with lavage of corrosive sublimate, followed by boiled water.

Putrid empyema is usually cured by thoracotomy.

Tubercular empyema is usually very slow. Thoracotomy may be dangerous, and is usually insufficient. Repeated aspirations at long intervals give the best results.

But Anthony (*ibid.*, p. 536) describes a case of pure culture pneumococcus empyema in which five successive punctures were made, each followed by an injection of betanaphthol. The size of the abscess cavity continually increased under this treatment.

Netter (*ibid.*, p. 487) reports two cases of Friedländer's bacillus capsulatus, in the first admixed with staphylococcus pyogenes aureus and albus, and in the second a pure culture. In the former, the empyema was secondary to the rupture of a large cavity in a tubercular lung with pneumothorax. The patient died. In the second there was complete recovery without operation, the patient raising pus by expectoration to the amount of 100 to 200 grams. The account of this case leaves the reader in doubt whether it could not have been a simple abscess of the lung without actual involvement of the pleura.

Netter also reports a case of hemorrhagic pleurisy containing a pure culture of the bacillus of Eberth, which has been found alone or with others in osteomyelitis, bronchopneumonia, purulent pleurisies, etc. This fluid when injected into the pleural cavity of the guinea-pig and some other animals caused a hemorrhagic exudation in them.

Prudden (*N. Y. Medical Journal*, June 24, 1893) records the results of the examination of forty-five cases of pleuritic effusion.

In twenty-one cases of serofibrinous pleurisy the exudates revealed bacteria in only two, and in these two cases, which were associated with acute lobar pneumonia, the pneumococcus was the only germ found.

In twenty-four cases of empyema the exudate revealed bacteria in all. In the cases of simple empyema, the germ most commonly present (in seven out of eight) was the streptococcus pyogenes. In the cases of metapneumonic empyema, the germ most commonly present (in nine cases out of eleven) was pneumococcus. In the four cases of fetid empyema, various forms of bacteria, mostly bacilli, were

found. Only once was staphylococcus aureus present. In the one case of tubercular empyema the tubercle bacillus alone was present.

The mortality in the cases of streptococcus was much higher than those associated with pneumococcus (five out of eight having died when streptococcus was present, as against two deaths out of eight in pneumococcus), and in both of these latter there was an inflammatory heart complication.

Staphylococcus pyogenes aureus or albus may exist in serum exudates without the latter developing pus. So may pneumococcus. But if streptococcus is present the exudate is very apt to become purulent, though in a few cases it has not done so.

While Netter's experience is that metapneumonic pleurisy is more apt to be purulent than serous (in proportion of eighteen to four), the other observers say that a smaller proportion than this get purulent.

Certain bacteria which are usually associated with some special form of disease are capable under other circumstances of producing less well-defined and distinctive lesions, *e. g.*, tubercle bacillus, which usually causes tubercular tissue, may cause pus. Pneumococcus, besides causing pneumonia, may cause meningitis, pleurisy, or phlegmon. So of bacillus typhosus and bacillus coli communis.

Ehrlich (*Charité Annalen*, 1880, vol. vii., p. 202) describes five cases of pleurisy with hemorrhagic exudates, all following puerperal sepsis, one at least of which produced empyema, and all of which contained organisms related to the primary infection.

A valuable paper by Koplik (*American Journal of the Medical Sciences*, July and August 1891) treats of the empyemas of children from a bacteriologic point of view.

This author gives a careful bacteriologic study of the exudate in fifteen cases of empyema in children. He found (except for the association of tubercle bacilli with streptococci) that the organism in each given case existed in a pure state, the pus being really a pure culture of one organism.

He divides them into four groups:

1. Streptococcus and staphylococcus. While he admits the possibility that these cases may have been of pneumonic origin, he is yet inclined to ascribe them to other causes, such as cold and wet.

2. Diplococcus pneumoniæ (Fränkel). In this category he places all metapneumonic cases.

3. Tuberculous. In the one case which Koplik places in this category he found tubercle bacilli, but also from the first streptococcus. He admits the difficulty in a large portion of such cases of demonstrating tubercle bacillus.

4. Empyema from suppuration in other parts of the body. Here a streptococcus was isolated, which was of exceptional virulence, differing in character as in causation from the streptococcus cases of Group 1. It caused profound sepsis in animals injected. He admits the possibility that even here a streptococcic (pyemic) pneumonia may have been intermediary between the original infection and the final empyema.

In two cases exudates originally sweet turned putrid after operation—one metapneumonic, one tubercular. Koplik points out that this is not due to the mere admission of air into the pleural cavity, or even to an infection brought on by the drainage-tube from the lips of the wound, for these conditions exist in all operated cases, but rather to retention of a large amount of pus from an unexpanded lung.

The present paper is based upon the study of 135 cases of empyema treated at the Boston City Hospital during the last six years, or from the time that Dr. Councilman has had charge of the pathologic laboratory.[1] The cultures were made from specimens withdrawn by needle after careful sterilization of the chest, the drop of pus usually being coughed out through the needle into a sterile tube. In most cases the organism afforded was the result of the culture. In a few cases it was determined morphologically, the growth being unsatisfactory. This was generally ascribed to the fact that the organisms were dying out of the exudate.

The 135 cases included 93 males and 42 females. The right side was involved in 54 cases, the left in 71. Ages of the patients were as follows:

	Cases.
Under the age of 10	15[2]
From 10 to 20	15
From 20 to 30	41
From 30 to 40	24

My acknowledgments are due to my colleagues on the medical and surgical staff of the hospital for permission to refer to their cases, and to Dr. Howard B. Jackson, house physician, for assistance in the labor of collating cases from the records of the various services.

[1] Of these, three died.

The oldest patient was sixty-five years old, the youngest five months.

Organisms present.	Cases.	Deaths.
Diplococcus lanceolatus alone	28	8
" " with others, unspecified	1	
" " with colon and pyocyaneus	1	1
" " with Friedländer	1	
" " with staphylococcus albus	2	
" " with staphylococcus aureus	2	
" " with staphylococcus citreus	1	
Streptococcus alone	35	9
" with lanceolatus	18	2
" with variety of others, unspecified	9	7
" with staphylococcus aureus	2	
" with staphylococcus albus and aureus	1	
" with saprophytes	1	
" with colon bacillus	2	
" with lanceolatus, S. aureus, and colon	1	
" with lanceolatus and colon	2	1
" with lanceolatus and S. albus	2	
" with lanceolatus and pyocyaneus	1	
Staphylococcus aureus	6	4
" albus	1	
" " and aureus	2	2
" " with others unspecified	1	1
" " with M. tetragenus	1	1
Pyocyaneus	2	
Friedländer	2	
B. typhosus	1	
Colon bacillus with others unspecified	1	
Sterile	9	2

In all

Diplococcus lanceolatus appears in	60
Streptococcus pyogenes appears in	74
Friedländer (twice in pure culture)	3

	Cases.
Pyocyaneus appears in	4
Pure	2
With lanceolatus and colon	1
With lanceolatus and streptococcus	1
Colon bacillus appears in	6
With pyocyaneus and lanceolatus	1
With streptococci	2
With streptococci, lanceolatus, and S. aureus	1
With streptococcus and lanceolatus	2

		Cases.
Staphylococcus aureus appears in		13
With diplococcus lanceolatus	2	
With streptococcus	3	
With streptococcus, colon, and lanceolatus	1	
With albus	2	
Alone	5	
Staphylococcus albus appears in		7
With aureus	2	
With aureus and streptococcus	1	
With lanceolatus and streptococcus	2	
With tetragenus	1	
Alone	1	
B. typhosus appears in pure culture in		1

Etiology. As some of the patients entered after having been ill several days, it is not always possible to be sure of the condition precedent to the empyema, but from the evidence of the record taken in connection with the physical signs, it appears that pneumonia preceded the empyema in the great majority of cases (80 certainly, and 15 more probably, or in all from 95 to 100). From this it will appear at once that the diplococcus lanceolatus has no distinct relation with the antecedent pneumonia, other organisms, especially the streptococcus, being as fully represented among these metapneumonic cases as is the diplococcus lanceolatus itself. The pneumonia was apparently also nearly always lobar. The period after the onset of pneumonia when pus was first detected in 96 of the cases averaged twenty-five days, the range being from six to sixty-six days. There were cases in which pus appeared after the onset of pneumonia at six, seven, eight, nine, and ten days. The longer periods may have been accounted for by failure to detect pus as early as it was formed. Some of the pneumonias were secondary to septic disease elsewhere, as, for example, cellulitis and abscess.

Tuberculosis was present in about twenty cases, and in a few of these acute pneumonia had supervened. Other causes of the empyema were typhoid fever (3 cases), puerperal infection (2 cases), appendicitis (1 case, eighteen days previous to the empyema), actinomycosis, tonsillitis, and otitis.

Operations were performed upon 115 of these patients, leaving 20 cases unoperated upon. Of the latter 10 died, all of them being adults. Five of these were cases of diplococcus lanceolatus, 2 of

streptococcus and lanceolatus combined, and 1 of streptococcus and aureus combined. Of the 10 unoperated cases which recovered, 8 cases followed pneumonia, 1 phthisis, 1 phthisis with pneumonia; 3 showed lanceolatus, 3 streptococcus, 1 pyocyaneus, 1 streptococcus and lanceolatus combined, 1 Friedländer, 1 lanceolatus and staphylococcus citreus combined.

Some of these cases were unsuitable for operation, for they seemed to be recovering, and the fluid withdrawn, while it contained pyogenic organisms, was not markedly purulent. Others were advised to submit to operation, but refused.

It will be noticed that in these two groups of the unoperated cases the lanceolatus was more prevalent in the fatal half of the cases; but here, as will be also observed in the discussion of the mortality of the whole series, it does not appear that any great stress is to be laid upon the particular organism. While those present in the cases of pneumonic origin are quite as likely to be streptococcus as pneumococcus, it is to be noticed that cases connected with suppuration or sepsis elsewhere than in the chest showed a marked tendency to the distinctly marked pus organisms. For example, of 9 such cases 3 were streptococcus, 1 streptococcus with an admixture, 3 aureus, and 2 aureus and albus.

Details of Operation on One Hundred and Ten Patients.

The site of incision was in 3 cases the anterior axillary line, in 17 the mid-axillary line, and in 47 the posterior axillary line. In 1 case it was behind the scapula. Seventeen of the operations consisted of incisions through the pleura without the resection of any of the ribs. Three times the fifth rib was resected, twice the sixth rib, 33 times the seventh rib, 20 times the eighth rib, 5 times the 9th rib, 12 times unspecified ribs, 3 times more than one rib was excised. The pleural cavity is recorded to have been irrigated one or more times in 46 cases, and it is specially recorded that no irrigation was practised in 34. The immediate effect of the operation was generally to reduce the temperature to a considerable degree, but this reduction was not always permanent. Sometimes the operation was followed by a marked rise of temperature, and this was generally of bad prognostic significance, although sometimes a rise of 3° immediately after opera-

tion gave way to a subsequent favorable temperature curve and improvement in the patient's condition.

The agent most commonly employed for irrigation was salt solution (9 times), next comes boric acid (8 times); potassium permanganate, hydrogen peroxide, and sterilized water were also used. No special difference in the results of the various fluids was noticed, nor was there any marked difference in the outcome of the cases which were irrigated and those which were not. The cases were retained in the hospital after operation, as a rule, until the drainage was able to be discontinued and the treatment continued in the out-patient department.

The average time required for this in 76 cases—that is, the length of hospital residence after the operation in non-fatal cases—was about thirty-two days. Of the 135 patients 92 left the hospital improved. A majority were well on the way to convalescence, a small amount of pus discharging from the opening, and the breathing heard down to the level. The subsequent history cannot be traced. In a few only the imperfect expansion of the lung gave reason to fear that the cure would not be perfect. In a number of instances the Wollfe bottles were used, in which the patient displaces a quantity of water from one bottle to another through a tube employed for the purpose of lung expansion.

In one patient there was a double operation (Case 30). Boy, aged ten years, developed pneumonia of the left lower lobe October 5, 1897; of the right lower lobe October 18th. White count, October 12th, 21,500; October 30th, 40,000. Pus was found in the left pleura November 8th. Operation thirty-three days after the onset of pneumonia by Dr. Munro. A Cabot grooved needle was introduced into the pleura at the lower end of the scapula, and the sound showed a cavity occupying one-half to one-fourth of the left chest, at the same time pleurotomy in the right side with the resection of the rib; cavity larger than on the left; no irrigation. Culture from each side showed lanceolatus. Both incisions had healed in twenty-four days.

Mortality. Of the 135 patients 40 died in the hospital, or 29 per cent. Of these, 5 were three years old or under. With this we may compare the—

Mortality According to Organisms.

Of the 35 patients having a pure culture of streptococcus 9 died, or 26 per cent.

Of the 18 having streptococcus and lanceolatus 2 died, or 11 per cent.

Of the 9 with streptococcus plus other organisms 7 died, or 77 per cent.

Of the 2 with streptococcus plus aureus 2 died, or 100 per cent.

Of the 28 pure cultures of lanceolatus 8 died, or 28 per cent.

Of the 2 with streptococcus, lanceolatus, and colon 1 died, or 50 per cent.

Of the 6 cases of staphylococcus aureus 4 died, or 66 per cent.

Of the 2 cases of staphylococcus albus 1 died, 50 per cent.

Of the 2 cases of staphylococcus aureus and albus 2 died, or 100 per cent.

Of the 2 cases of Friedländer neither died.

Of the 9 sterile cases 2 died, or 22 per cent.

It will be seen from the foregoing figures that our experience does not bear out the statement made by Netter and others, referred to in the beginning of this paper, of the relative mildness of the lanceolatus cases and the gravity of the streptococcus cases, as the mortality from lanceolatus is slightly greater than that from streptococcus. The mixed infections on the whole appear more fatal than those of a single organism.

Of the 5 children under three years of age who died, 3 had streptococcus and 2 staphylococcus aureus.

So far we have considered the mortality as represented only by cases dying in the hospital, but the subsequent history of the other cases cannot be traced. Many were very nearly well; some, though much relieved, were not "well," and a few probably went into a lingering decline.

After a pretty careful examination of the records, I have selected five more cases which probably should be added to the list of fatalities, their condition being such that it is doubtful if they ever recovered. This would make a total mortality of 45, or 33 per cent.

It may be interesting, taking these 45 cases with their bacteriologic contents, to compare the contribution made to the death list by each

organism or combination of organisms with the proportion which they respectively represent of the grand total of cases.

	Fraction.	Per cent.
Streptococcus furnished of all deaths . . .	11/45	24
" " of all cases . . .	37/135	27
Lanceolatus furnished of all deaths . . .	8/45	18
" " of all cases . . .	28/135	20
Streptococcus with lanceolatus, of all deaths .	3/45	7
" " of all cases .	19/135	14
Streptococcus with other admixtures, of all deaths	8/45	18
" " " of all cases .	10/135	7
Staphylococcus aureus, of all deaths . . .	4/45	9
" " of all cases . . .	6/135	4
Staphylococcus aureus with admixtures, of all deaths	4/45	9
" " " of all cases	4/135	3
Other admixtures, of all deaths	5/45	11
" " of all cases	12/135	9
Sterile exudates, of all deaths	2/45	4
" " of all cases	9/135	7

No importance is attached to this last, as some of the exudates probably owed their sterility to the organisms having died out.

It will be seen that the first three of these groups—viz.: streptococcus, lanceolatus, and the combination—figure lower in the death list than in the whole number of cases—that is, they show a relative advantage in the matter of recovery; while the next four groups—viz.: the streptococcus with mixed infections, and the aureus alone and admixed—show a relative disadvantage—that is, contribute more heavily to the death list than their numerical importance would warrant.

Hence, single organisms and the combination of streptococcus and lanceolatus are more favorable than the other mixed infections.

A more careful examination of the fatal cases shows that other conditions are of much greater significance than the variety of organism present. For example, suppurative processes in or outside of the chest were very frequent.

(*a*) In the chest there was abscess of the chest wall in 1 case, fetid pus or gangrene in the lung in 3, pyopneumothorax in 3 cases, 1 of which died from hemorrhage of the wound and 1 from hemorrhage of the lung; actinomycosis in 1 case.

(*b*) Outside of the chest: Septic inflammation of the hands and feet in 5 cases, 1 of which had also carbuncle of the hip. Parotid abscess in 1 case, suppurative otitis in 1 case; general peritonitis and abscess below the diaphragm in 1 case; purpura hemorrhagica in 2 cases; multiple injuries in 1 case.

(*c*) Other diseases: Sarcoma of the lung in 1 case; croup (no Klebs-Loeffler bacillus found), 1 case; aortic insufficiency, 1 case; mitral insufficiency, 1 case; chronic diffuse nephritis, 1 case; typhoid fever, 2 cases. In the last, bacillus typhosus was especially looked for in the exudate, but none was found.

Ten of these patients died unoperated upon. In one, operation failed to reach pus, and in another the first operation failed to reach pus and the second one succeeded, only as the patient was moribund.

Of the 30 fatal cases which had a free opening of the chest wall 7 died upon the table or within a few hours. Eliminating the case of sarcoma of the lung, which survived the thoracotomy for three months, the average duration of life after the operation in the other fatal cases was about nine days. In several patients the immediate cause of death was undoubtedly pneumonia, a definite extension of the consolidation being observed after the operation, sometimes to the opposite lung. In some of the cases postmortem examination confirmed this extension of the pneumonic process.

Of the fatal cases the following are especially deserving of mention:

Actinomycosis (Case 16). Female, aged forty-eight years. Swelling on and under the left breast. Considerable foul pus in the pleura, sterile. Operation by incision, and removal of the large actinomycotic masses found at the operation. Patient improved for ten days; died seventeen days after the operation. Autopsy showed the right lung normal; left lung compressed, completely solid, intimately adherent to the pleura and chest wall, so that masses had to be torn away. On the pleural surface was a dense fibrous tissue mass one-half centimeter in thickness. Sinuses from the pleura to the left mammary region.

Sudden Death without Operation (Case 22). Female, aged thirty-eight years. Four weeks after lobular pneumonia first aspiration withdraws seven ounces of green pus from the left chest. Temperature reduced 2°. Second aspiration a few days later was followed the next day by the sudden death of the patient. Cause unknown. No autopsy.

Typhoid Fever (Case 20). Male, aged thirty-seven years. Typhoid fever; Widal test positive, etc. Twenty-fourth day, chill; twenty-fifth day, phlebitis of left leg; forty-fifth day, pus by aspiration; a few days later perma-

ment opening. Streptococcus pus. Ten days after this pus broke into the bronchus; bloody purulent expectoration; temperature rose to 108°. Death eighteen days after operation, sixty-five days after the onset of typhoid.

(Case 107.) Widal test positive. Lobar pneumonia on the eighth day of typhoid, with chill; twenty-nine days after pneumonia 300 c.c. of bloody seropus aspirated from the left chest. Streptococcus pyogenes and staphylococcus aureus. No incision of chest wall. Patient died the day after the aspiration.

Compare with these the third case of typhoid (Case 64); not fatal:

Male, aged thirty-four years. Twenty-eight days after the onset bloody pus was aspirated from the left chest. B. typhosus. Operation twenty-two days later; rib resected. Drainage for sixty days. Patient discharged nearly well seventy-five days after operation, one hundred and twenty-five days after the beginning of typhoid.

Pyopneumothorax; Abscess of the Liver (Case 34). Male, aged thirty-six years. Right renal calculus two years previous. Taken sick January 2d; ten days later one pint of pus was aspirated from the right chest; streptococcus and diplococcus lanceolatus. Ten days later signs of pneumothorax; eighth rib resected. Finger showed communication of empyema through the diaphragm into the abscess cavity of the liver. Patient died in three hours.

Gangrene of the Lung (Case 38). Male, aged fifty-six years. Grippe about Christmas, with pneumonia (?). After recovery worked two weeks, and had to give up. Fifty-eight days after the grippe pus was drawn from the right chest; two days later the patient died. Autopsy showed healed tuberculosis of the left lung, consolidation of the right upper lobe, gangrenous area 3 cm. in diameter communicating with bronchi; also independently an abscess of the lung communicating with the pleura. Contents of the pleura very fetid, containing great variety of organisms.

Purpura Hemorrhagica (Case 63). Female, aged thirteen months. Entered hospital July 11th. Three weeks before left ankle swollen without redness; pain on motion; swelling rapidly extended up the leg; leg constantly cold. This morning swelling of the right hand. July 15th, punctate hemorrhages over the trunk and neck. July 19th, left hand swollen, right foot bluish, few hemorrhagic spots over the right costal margin. Marked edema of the skin over the left side; upper left front of the chest flat, extending down into the axilla; signs of fluid; gradual extension of hemorrhagic spots over the body. July 26th, chest bulging; aspirated nine ounces of green pus; staphylococcus pyogenes aureus; spots increasing over the whole body. July 27th, head retracted; no operation on chest wall attempted. August 1st, bleeding from the gums; more bleeding into the skin. August 3d, external strabismus. Died apparently from intracranial hemorrhage.

(Case 71.) Female, aged thirty-nine years. Phthisis; exudate thin; odorless pus: staphylococcus aureus and albus. Day after the operation purpuric spots were seen over the body. Died second day after the operation.

Sarcoma of the Lung (Case 101). Female, aged fifteen years. Leg had been amputated at the hip for sarcoma some time previously; pneumonia. On the twenty-third day, pus in the pleura; immediate operation; resection of the fifth rib in the right anterior axillary line. Right chest gradually grew larger; repeated aspirations failed to detect any more fluid. The patient gradually failed, and died ninety-seven days after the operation. No autopsy.

Pulmonary Thrombus (?) (Case 113). Female, aged eleven years. Patient had septic hand March 1st, septic foot March 14th; cough, pain, and fever on same date. March 21st, operation upon the hand and foot; irregular temperature. April 4th, operation on the right pleura; fifth rib outside the nipple excised; much cloudy serum, containing staphylococcus aureus. Same organism had already been present in the pus removed from the hand and foot. Spleen and liver enlarged, the latter reaching nearly to the umbilicus. There being evidence of retained pus April 30th, a trocar was inserted in the eighth interspace anterior to the axillary line; it penetrated the liver; no pus. Trocar inserted again in the back into the pleura, withdrawing a little serum. Then the old track was explored and a little retained pus extracted. White corpuscles, 17,000. May 8th, tenderness over the right calf and femoral vein. May 9th, died suddenly, thirty-six days after the first empyema operation, and forty-nine days after the onset of the empyema. Cause of death believed to be pulmonary thrombosis. No autopsy.

Perforation into Bronchi. The general unfavorable significance of this occurrence is confirmed by our experiences. Such a perforation took place in 12 cases. Of these, 7 died in the hospital and 2 were discharged not much relieved. In 5 of these there were streptococci with other organisms—in 1 case the combination being with saprophytes, in 1 staphylococcus albus, in 2 lanceolatus, and in 1 lanceolatus pyocyaneus and colon. The 3 remaining cases of the 12, which were probably recoveries, had streptococcus, Friedländer, and an exudate which was sterile.

Pulsating Empyema (Case 9). Female, aged nineteen years. Entered hospital December 30th, four days after an acute attack of pain in the left chest, though cough had existed for a few weeks before. Aspirated, January 2d, 24 ounces of clear serum. High temperature continued, with oscillations of 4°, the patient refusing to be aspirated again until February 16th, when there was a dry tap, though needle felt free in the pleural cavity. On March 2d a slight bulging was noted at the third space in front; also two similar spots found in the seventh and eighth spaces in the axilla, all pulsating synchronously with the heart-beats. At one of the lower spots the needle was introduced and 30 ounces of pus removed; streptococcus. This stopped both bulging and pulsation. Further operation refused, but accepted later,

and on March 10th the seventh rib was excised. After this the temperature came down to 99–100°, with slight oscillations, except for two or three days, when there was a range of 2½°. Discharged thirty-nine days after operation, with sinus nearly healed, no pulsation, but breathing heard only to the third rib.

Gangrene (Case 130). Male, aged forty-two years. Lobar pneumonia, followed by profuse, fetid expectoration. Leukocytosis at beginning of the empyema, 11,000; 7200 when pus was found in the chest. At the time of operation a gangrenous mass of large extent was found in the lung and scooped out. The temperature came down, and so continued, except on the forty-fifth day, when the patient had a fever, lasting four or five days, with signs of consolidation in the right upper lobe. Examination of the chest fifty-three days after the operation shows good breathing in the right chest in front to the base on the mammary line. In the axilla the breathing is absent below the level of the nipple. Behind, breathing is good to the mid-scapula, but below this is scanty. Air is expelled through the opening by cough.

Penetration of Pus below Diaphragm (Case 97). Female, aged twenty years. Tubercular pleurisy two months; tubercular focus in left apex. Patient cannot raise the left arm. Foul pus aspirated. Operation. Discharge remained excessive; streptococcus, lanceolatus, and colon-like bacillus. Patient died twenty-five days after the operation. Autopsy showed empyema, localized peritonitis, subphrenic abscess, perisplenitis.

Purulent Otitis Media (Case 135). Male, aged one year. Subacute otitis media. Twenty-three days afterward thick pus in the pleura; staphylococcus pyogenes aureus. Twenty-five days after aspiration, operation with resection of the eighth rib. On the second day the temperature rose to 104°, where it continued until death, on the seventh day. On the sixth day, there being evidence of retained pus, ten or twelve punctures were made over the flat area in the back; no pus obtained. The last puncture entered the stomach. Autopsy showed 100 c.c. of very turbid puriform fluid in the pelvis. Considerable recently-formed fibrinous exudate about the liver, spleen, and hollows of the greater or lesser peritoneal cavity. Left pleura uniformly thickened 1 to 3 mm. Posterior half of the left pleural cavity entirely obliterated by chronic dense fibrous bands. Complete atelectasis.

Leukocytosis. Cases of pneumonic origin had the leukocytes belonging to that condition, and the change in the white count due to the supervention of empyema was not marked nor constant. In some cases there was a fall in the white count and in some a rise; for example, Case 83 had lobar pneumonia April 27th. May 4th the white count was 25,600; May 16th pus was discovered, streptococcus and pneumococcus, and the white count on that day was 14,800.

On the other hand, Case 82 had lobar pneumonia April 16th.

White count May 5th, 23,200; May 15th, 31,400; May 16th, streptococcus pus aspirated. Operation refused. Patient discharged seven days later, temperature of the last four days having been nearly normal.

Chronic Sinus with Retained Foreign Body (Case 11). Male, aged eighteen years. Was operated upon for empyema May 19, 1896. Rib not resected. Discharged, relieved, thirty-two days later to the out-patient department. Second operation April 16, 1897. Sixth rib resected, followed by a rise of temperature and irrigation. Discharged in twenty days, relieved, to the out-patient department. Third operation two years later. Exostosis of eighth and ninth ribs, which were both resected. A rubber drainage-tube was found in the pleura, which had been lost after one of the previous operations. Cavity curetted. Discharged, relieved.

Discharged Gastric Contents (Case 15). Male, aged seven years. Green, foul pus five weeks after lobar pneumonia; bacillus coli communis, and others. Resection of the seventh rib at mid-axillary line. Records state that for about ten days the wound discharged fluid apparently containing gastric contents. Patient discharged thirty days after the operation. Moderate purulent discharge. General condition improving.

Consecutive Aspirations with Development of Pus. Our experience coincides with that of other observers in having noted several instances in which an exudate, originally clear serum, has gradually become purulent. For example, Case 45 thirteen days after lobar pneumonia had clear serum in the pleural cavity, containing, however, streptococcus. One week later the fluid still contained streptococcus and also pus.

Case 119, twenty-nine days after lobar pneumonia, had one ounce of straw-colored fluid containing pneumococcus. Eight days later the fluid was seropurulent; culture, pneumococcus. Thirteen days later the patient was moribund; fluid purulent. Here the leukocytes diminished from 38,000 on the fourth day of pneumonia to 21,000 during empyema.

(Case 123.) Lobar pneumonia March 29th; aspirations April 16th and 29th and May 20th. The latter one was diplococcus lanceolatus. Patient declined operation and left the hospital nearly well.

In some cases the consecutive aspirations indicated a change in the organisms present; for example, Case 111 was tapped repeatedly, following a lobar pneumonia, and sterile serous fluid was obtained. Finally, seven weeks after pneumonia, the exudate contained staphylococcus pyogenes aureus.

Again, Case 77 had lobar pneumonia February 1st. Aspirated March 2d, clear sterile fluid; again, March 7th, the same; March 14th, clear fluid, but blood-stained. Staphylococcus aureus and albus. Next day pus from both ears. Again, March 25th, brown pus in the pleura. Immediate operation. Temperature very septic. Patient died on the seventeenth day.

Subdiaphragmatic Abscess with Secondary Purulent Pleurisy. The two following cases are not included in the 135 cases previously discussed, because the infection started from below the diaphragm, but they may be mentioned here as having points of interest in this connection.

The first was a collection of pus below the diaphragm, and an aspirator needle was introduced in the ninth space in the left anterior maxillary line. It was subsequently found to have penetrated the stomach, which shows that care must be taken in aspirating at a point so low down and so far forward. The autopsy showed pus below the diaphragm, with secondary abscess of the lung.

The second case was that of an Italian, aged thirty-five years, who, in November, 1898, had an attack of diarrhea, lasting one month, followed by pain for a week, then a return of the diarrhea. April 3, 1899, bulging of the ribs on the right and tenderness with dulness below the level of the nipple. One inch of the ninth rib was excised in the mid-axillary line. Several quarts of thick pus was evacuated. Abscess seen to be subphrenic. Patient died on thirteenth day. Autopsy showed healing diphtheritic ulcers of the colon, abscess of liver, and empyema. The operation wound entered the abscess between the liver and diaphragm; the upper end of the operation wound entered the pleural cavity, so that the tip of the finger can pass from the peritoneal to the pleural cavity. The pleural exudation was supposed to be caused by infection through this opening. Unexpanded lungs.

In varying patients a great difference is noted at the time of operation in the matter of expansion of the lung, and this difference is not always easily accounted for. Sometimes the lung expands immediately, and then contracts again; sometimes it does not expand at all. It is generally supposed that non-expansion is more likely where the pressure upon the lung has been long continued, but this is not always true.

In Case 132, a healthy young man of twenty-one years of age, with lobar pneumonia, pus (streptococcus) was detected exceptionally early—namely, on the fourteenth day, and an operation was done on the fifteenth day, with a resection of the seventh rib; an examination of the patient on the fifty-fourth day after the operation showed a marked shrinkage of the chest

wall, but a great interval between the outside of the lung and the inside or the pleural cavity—that is, no expansion had occurred.

It seems reasonable to suppose that the early operation in this case, before the pneumonic process had given way to resolution, may have hindered lung expansion.

The conclusions which I have drawn from the study of these cases are the following:

Empyema, while capable of being caused by manifold infections within and without the chest, is in the majority of cases the result of pneumonia. The variety of the pneumonia is not to be judged by the organism present in the empyema; for as it has been shown by Weichselbaum that even in lobar pneumonia other organisms, notably the streptococcus, may be present in the lung as an admixture of the one which we consider the specific cause of lobar pneumonia, viz., the lanceolatus of Fränkel, there is an opportunity for that contaminating organism to penetrate to the pleura. The lanceolatus, if present, may probably be taken to indicate a previous pneumonia, but the streptococcus, if present, may equally indicate a lobar, lobular, or grippal pneumonia, or a phthisis with mixed infection. As tuberculosis has greater malignancy after it acquires a mixed infection, so it may be that these lobar pneumonias in which a streptococcic contamination is most marked are the ones most liable to produce an empyema, and that the organism in the purulent exudate is as likely to be the contaminating as the original infection.

When the streptococcus is due to suppurative or pyemic conditions outside the chest, it is probably of a more virulent type, and has a correspondingly bad prognosis. But in the metapneumonic cases the prognosis of streptococcus seems to be no worse than that of lanceolatus.

The great difficulty in securing the healing of operated cases is in bringing the opposite pleural surfaces into permanent contact. When the lung does not fully expand (as is usually the case) the thoracic wall must go in to meet it. This is one reason for the free resection of the ribs, and the relatively favorable prognosis in childhood is due in part to the greater liability of a soft and flexible chest wall to contract upon the lung.

Some cases certainly recover without operation. It is difficult to determine in advance which these will be. The particular organism

present, if a pure culture, is a less cogent factor in determining the need of operation than the fever, prostration, chills, the quantity of pus cells present, and the tendency to refill after aspiration.

The gradual development of pus after successive aspirations can usually be forecast from the presence of streptococci or pneumococci in the first fluid withdrawn, even though that be a clear serum. But pus may appear when the early tappings are sterile—perhaps from a later infection from within the lung.

A needle introduced into the same intercostal space in two patients may in the one case enter the pleural cavity and in the other the stomach, according as the diaphragm is arched up by fluid below it or pressed down by fluid above it. Hence the importance of diagnosing empyema from subphrenic abscess.

Perforation of an empyema into a bronchus from undue delay in operation is a dangerous condition. But the opening of the thorax while an underlying pneumonic consolidation is still unresolved is not conducive to ready expansion of the lung, and a moderate delay of the thoracotomy till the pneumonia has resolved, meantime keeping down undue compression by an occasional aspiration of the pus, is a conservative procedure.

DISCUSSION.

DR. WELCH: I should like to say a word about this subject, in making sure whether a case is due to the streptococcus or to the lanceolatus. Of course, the majority can be easily determined, but there are intermediate cases where one might be in doubt. At least that has been my experience, and it requires a very careful examination, morphologically and by the inoculation of animals, to settle the question. It is well known that the streptococcus may grow in chains and be encapsulated so that their recognition is difficult. Dr. Withington did not indicate whether he had encountered such difficulties, but I am sure they occur.

DR. PRUDDEN: I may add that I have come to regard as unreliable many of the earlier statistics of bacterial species present in the exudate, since the presence of a capsule is not as important as was formerly believed in the differentiation between pneumococcus and streptococcus.

DR. KOPLIK: I was rather surprised at the large proportion of so-called pneumonic cases in the adult, and I think it is possible that some of the

streptococcus cases may have been included in this list. It is also possible that a number of cases in which streptococci alone are found are tuberculous.

DR. OSLER: I should like to ask whether the author has any figures pointing to a great increase of empyema following pneumonia during the past five or ten years. In the figures published by Dr. White, from Guy's Hospital, it is shown to be nearly double that of the period previous to that time. I think our experience is much the same, and I believe Dr. Hale White attributes it to the prevalence of influenza.

DR. JACOBI: I understood the doctor to say that when he found either of these organisms alone he gave a bad prognosis, but that when he found both together the prognosis was good. What is the explanation for this?

DR. WITHINGTON: I may say that this series was considered during the time when Dr. Councilman was in charge of the laboratory, and the work was done by one of his assistants in a most careful manner, and I believe has been generally accepted by the clinicians. In only a few cases, perhaps, was the work simply a morphologic examination, cultures being made in most instances.

In regard to Dr. Osler's question, I think there can be no doubt about the relative increase of empyema lately, for in going over our books we found the majority of cases to have occurred during the last two years, and in my own experience I find its occurrence vastly greater this past year than even the year before.

In regard to Dr. Jacobi's question, the prognosis does not seem to be absolutely bad in either instance, but where the two organisms are obtained together it is rather better. And the only explanation I know is that the combination is less deadly.

A STUDY OF BACTERIAL CELLS.

(The Rockefeller Research in the Hygienic Laboratory of the University of Michigan, 1902.

PART I.—INTRODUCTION.

By VICTOR C. VAUGHAN, M.D., LL.D.,
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After it had been demonstrated beyond controversy that certain bacteria cause certain diseases, quite naturally the question was asked, How do these micro-organisms cause disease? Several answers to this question have been offered. If the liver, spleen, or kidney of a guinea-pig which has died from experimental anthrax be sectioned and examined under the microscope, the bloodvessels of these organs will be found to be filled with bacilli. In many places it will be observed that the germs have grown so abundantly that they distend the smaller bloodvessels. It was suggested that the anthrax bacillus causes disease and death by mechanically interrupting the functions of certain organs. This is known as the mechanical interference theory. It was at one time suggested by Toussaint[1] that the symptoms and death in anthrax are due to stoppage of the pulmonary circulation by means of emboli, but numerous postmortem examinations fail to confirm this view. In the majority of germ diseases this theory never had any support, because there is not found any great accumulation of bacteria in any organ, and the number and distribution of the micro-organisms are such that the theory of mechanical interference cannot be held. Another theory, at one time suggested, supposed that the bacteria cause disease by consuming the proteids of the body, and thus depriving it of its sustenance. It is known that the proteids are necessary to the building up of animal cells, and it is also known that micro-organisms feed upon proteids. This theory is untenable, in the first place because in

many of the infectious diseases life is destroyed so quickly that the fatal effects cannot be presumed to be due to the consumption of any large amount of proteid substance; secondly, the distribution of the germs in the body is such in many diseases that they do not come in contact with any large percentage of the proteids of the body; and thirdly, the symptoms of the majority of the infectious diseases are not those which would be produced by withdrawing from the various organs their food supply. In other words, the symptoms are not those of general starvation. A third theory suggested that the germs cause the symptoms of the disease and death by depriving the red blood corpuscles of their oxygen. This theory was proposed by Bollinger,[2] who was impressed by the resemblance between the symptoms of anthrax and those of carbon dioxide poisoning. The most prominent of these symptoms are dyspnea, cyanosis, convulsions, dilated pupils, subnormal temperature, and in general the phenomena of asphyxia. Moreover, postmortem examination reveals conditions similar to those observed after death by deprivation of oxygen. The veins are distended, the blood is dark and thick, the parenchymatous organs are cyanotic, and the lungs hyperemic. These are the symptoms and postmortem findings of apoplectiform anthrax, which Bollinger compared with poisoning with hydrocyanic acid, and it was at that time believed that this agent produces fatal results by robbing the blood of its oxygen. This theory found some support in the observations of Szpilman,[3] who ascertained that while the putrefactive bacteria are destroyed by ozone, the bacillus anthracis thrives and multiplies in this gas. This theory presupposed a large number of bacilli in the blood, and this accorded with the estimate of Davaine,[4] which placed the number at from eight to ten millions in a single drop, but more extended and careful observations showed that the blood of animals, dead from anthrax, is often poor in bacilli. These and other investigations of similar character caused workers in this field of research to doubt the truth of the theory, and these doubts were soon converted into positive evidence against it. Thus the theory that germs destroy life by depriving the blood of its oxygen has been found not to be true for anthrax, and if not true for anthrax, certainly it cannot be for any other known disease. The bacillus anthracis is, as has been stated, aerobic, while many of the pathogenic bacteria are anaerobic; that is, they live in the absence of oxygen.

This element is not necessary to their existence, and, indeed, when present in large amount, it is fatal to them. Moreover, in many diseases the bacteria are not found in the blood at all, and lastly, the symptoms of these diseases are not those of asphyxia. These facts have caused all bacteriologists to acknowledge that this theory is not the correct one. Next, it was suggested that bacteria cause disease by forming chemical poisons. This is the theory which has found general acceptance, and which is now believed to be the true explanation, although none of the specific toxins have been isolated in a state of chemical purity. The elaboration of chemical poisons by bacteria may occur in either of two ways: the bacterium acting either as a ferment or by forming some soluble enzyme may split up the proteids or other constituents of the body or of the artificial culture medium, and among these split products poisons may be produced.

According to this theory the formation of the specific toxin would be due to analytical processes. In confirmation of this theory, highly poisonous bodies have been found in artificial culture media of some of the pathogenic bacteria. Some of these poisonous bodies first found are basic in character, and are known as ptomains, a designation given to putrefactive alkaloids. Many chemists have sought diligently among the basic products of putrefaction for the specific toxins of the infectious diseases, and, while a few highly poisonous ptomains have been found, it is safe to say that no one has yet been discovered to which all of the symptoms and lesions of a disease could be attributed. The researches of Roux and Yersin,[5] followed by those of Brieger and Fraenkel,[6] on the diphtheria toxin, led to the conclusion that the specific poisons, instead of being basic in character, are modified proteids, and to these the term toxalbumin has been given. However, competent workers have failed to find toxalbumins in cultures of many of the most virulent pathogenic bacteria. Anthrax is the disease to which all the theories concerning the *modus operandi* of bacteria have been referred, and although Brieger and Fraenkel thought at one time that they had found a specific toxalbumin in the bodies of animals dead from anthrax, more careful examinations by other chemists have failed to confirm their results, and it is safe to say that no specific bacterial toxin belonging to this class of poisons has been found, either in the body after death from an infectious disease or in artificial culture media.

The other possible explanation of the production of chemical poisons by pathogenic bacteria is that these substances are formed by synthetic processes, and are built up in the cells of the micro-organism. The problem which I have attempted to solve, with the aid of my students, is that of determining whether or not the cells of pathogenic bacteria contain specific poisons. By means of the large incubating tanks, devised by myself, and which have been described and figured in the TRANSACTIONS OF THE ASSOCIATION OF AMERICAN PHYSICIANS for 1901, we have obtained the cellular substance of pathogenic bacteria in large amount, and with the material thus secured we have made the experiments detailed in this communication. Our studies have not been confined to a search for toxins, and we have attempted to make a contribution to the broader study of cellular chemistry. Incidentally we have been enabled to study some of the bacterial pigments which, in our tank growths, we have obtained in large amount.

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PART II.—A PRELIMINARY REPORT ON CERTAIN BACTERIAL PIGMENTS.

BY ANDREW J. DETWEILER, A.B., M.D.,
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INTRODUCTION. Since the nature and pyhsiologic importance of chlorophyl has been ascertained, scientists have become more deeply interested in other pigments found in the vegetable world, and within recent years botanists have given some study to the bacterial pig-

ments. Attempts have been made to learn more about their chemical nature, and the classification of pigmented bacteria has been attempted. Beyerinck[1] divides pigment bacteria into the following classes: 1. Chromophore bacteria, in which the pigment is an integral part of the cell body, in much the same way as chlorophyll exists in the chromatophores of higher plants and hemoglobin in the red blood cells. As examples of chromophore bacteria, Beyerinck mentions the sulphur containing purpurin organisms described by Ray Lancaster and others, and the non-liquefying green, yellow, and brown micro-organisms found in water. He thinks that in all of these chromophore bacteria the pigment performs a definite physiologic function, though he admits that at present we know but little about the subject. 2. Chromophore bacteria, or those which in young growths are colorless, but which excrete a chromogen that is converted into a pigment. Beyerinck regards the chromogen formed by this class of bacteria as an excretion product. In this class he places the bacillus prodigiosus, and he supposes that the chromogen excreted by this organism is immediately, or at least speedily, converted into a pigment which combines with albuminous substances, which are also products of bacterial activity. In the same class he places bacillus cyaneofuscus, bacillus cyanogenes, bacillus pyocyaneus, and bacillus virescens. He states that the chromogens formed by these different organisms vary in their diffusibility, and that they are oxidized into pigments which become fixed upon albuminous substances. 3. Parachromophore bacteria are those in which the pigment is undoubtedly an excretion product. In this class he places bacillus violaceus and bacillus ianthinus.

According to Beyerinck, a chromophore bacterium grows only as a pigment organism, while a parachromophore bacterium may produce either colorless or colored growths, according to circumstances. He states that in order to obtain a colored culture of the bacillus violaceus one must grow it under certain definite conditions, such as a low temperature, and that the culture medium must contain only small quantities of phosphates. On the other hand, the non-liquefying red and yellow micro-organisms, found in water, always show their characteristic colors, whatever may be the condition under which they are grown.

A chemical classification of the bacterial pigments has been at-

tempted. Thus Zopf[2] has studied certain bacteria pigments which he classifies under the head of lipochromes. Similar substances are mentioned incidentally by Krukenberg.[3] Other investigators have been led to believe from their researches that some of the bacterial pigments are identical with or at least similar to the anilin dyes. This view is held by Erdmann,[4] Bordoni-Uffreduzzi,[5] and Scheurlen.[6] Beyerinck believes that the pigment formed by his bacillus cyaneofuscus is identical with indigo blue. It will be seen from this that so far as previous investigations have been carried out, bacterial pigments may belong either to the lipochromes, the anilin dyes, or the vegetable indigoes.

The term lipochrome was recommended by Krukenberg[18] as a substitute for that of Fettfarbstoffe, which had been previously employed by Kühne and others. Lipochromes have been found and studied in the retina by Kühne and Ayers,[7] and by Capranica;[8] in the yelks of eggs, in blood, and in the shells of mussels by Städler,[9] and Maly;[10] and in the blood of molluscs by Halliburton.[11] Krukenberg[12] attempts to show that there is a relationship between lipochromes, melanins, bilirubin, and hemoglobin. In fact, he gives a diagram, which, however, is largely theoretic, in which he attempts to show how these bodies may be related to one another chemically. According to Zopf,[13] many bacteria contain lipochromes. He refers especially to staphylococcus rhodochrous, staphylococcus erythromyxa, and bacterium chrysogloia, all of which have been discovered and investigated by himself. From his bacterium egregium he states that he has isolated a lipochrome.

The Pigment of the Bacillus Violaceus. The germ substance of this organism was obtained in large quantity by growth in the incubating tanks. The germs were scraped off the agar with glass rods and the material thus obtained was repeatedly extracted with 96 per cent. alcohol. The alcoholic extract, having a deep violet color, was filtered and evaporated on the water bath. It was found that this solution could be boiled indefinitely without change in color. After evaporating the alcoholic extract, the residue was extracted with absolute alcohol, filtered, and again evaporated on the water bath. This left a greasy, bluish residue, having the consistency of a syrup. When applied to paper it produced a translucent grease spot, staining the paper slightly bluish violet. The residue was dried

on the water bath, and then in vacuo over sulphuric acid. When heated with potassium acid sulphate it yielded acrolein. There was no tendency to crystallization. The pigment was found to be slightly soluble in ether, to which it imparted a purplish violet color. Thinking that possibly the fat was only a contamination, I placed some of the alcoholic residue in a Soxhlet extractor and treated it with ether for several days. The distillate had a purplish violet color, but on evaporation on the water bath left a residue which soon turned light brown. From the portion insoluble in ether I obtained the acrolein test readily. The part insoluble in ether formed a bluish substance which did not change in color after prolonged heating on the water bath. The part soluble in ether did not contain any nitrogen, while the portion left after extraction with ether did contain this element. Believing that the nitrogen was due to contamination, I tried various methods to get rid of it. Finally I discovered that if the bluish violet residue was extracted for some time with petroleum ether, the nitrogen could be entirely removed, while the petroleum ether was colored slightly orange yellow. When the purified alcoholic residue was redissolved in alcohol and again concentrated it showed no tendency to crystallize, but yielded the same greasy substance. I attempted to saponify the fatty residue, but found that when sufficient alkali was added, the solution became first bluish green, and finally brown. On heating the coloring matter with the alcoholic solution of potash and evaporating, a brown-colored soap was obtained, but I was unable to completely remove the soap from the pigment. In fact, the amount of pigment removed from the soap by the solvents employed was so small that I gave up further attempts of purification by this method. It might be stated here that Kühne and Ayers had the same difficulty in separating the oily material from the pigments of the retina. Zopf also tried saponification without securing a satisfactory result. The pigment obtained by evaporating the alcoholic solution and washing the residue with petroleum ether is the purest form in which I was able to obtain it. In this condition it is readily soluble in ethyl and methyl alcohol, slightly soluble in amyl alcohol, and readily soluble in acetic acid. It is sparingly soluble in ether, forming a purplish solution. It is insoluble in water, petroleum ether, benzol, carbon bisulphide, and chloroform, and, as stated above, it contains no nitrogen.

When concentrated sulphuric acid is added to an alcoholic solution of the pigment it becomes first bluish, then green, and finally brown, and when an ether extract is carefully added to a small quantity of concentrated sulphuric acid, a like change in color follows. This is also observed when sulphuric acid is added directly to the pigment residue, but in this case the intervening colors, blue and green, are not easily distinguished, and the final brown appears quickly. When fuming nitric acid is added to the pigment residue, it quickly changes to brown, and a similar effect is caused by the addition of concentrated hydrochloric acid; but in the latter instance the changes proceed less rapidly. The caustic alkalies and barium hydrate induce the same change in color, but a saturated solution of sodium carbonate has no effect upon the color of the pigment.

When the brown or amber color is produced by either an acid or an alkali, careful neutralization will restore the original violet, but if the neutralization point is passed the brown color is again produced. Iodin in potassium iodid solution changes the pigment to a bluish green, then green, and finally light brown. Acetic acid does not change the color. Zinc and acetic acid produce a colorless solution, which, when shaken with the oxygen of the air, regains its original color. The restoration of the original color after reduction with nascent hydrogen may be more rapidly accomplished by the careful addition of the yellow oxid of mercury. Oxidation with free chlorin produces a dark amber color.

In attempting to crystallize the pigment I tried, along with other methods, the one suggested by Thudicum,[14] who employed mercuric acetate. I dissolved the pigment in glacial acetic acid, and to this I added mercuric acetate dissolved in acetic acid. When these two solutions were mixed, immediately there appeared at the place of contact a light brown color, and when an excess of the mercuric acetate solution was added the whole became brown. However, if only a small portion of the mercuric acetate solution was added and the whole mixture agitated, the blue color remained. This mixture was heated over a free flame until quite concentrated, and allowed to cool, when a finely granular deposit formed. Under the microscope these granules were found to consist of highly refractile, transparent particles of pale blue color. When heaped together in masses they appeared dark blue. Microscopically two forms were distinguishable.

One of these seemed to be very minute cubes, while the other consisted of ovoid forms. This incomplete and unsatisfactory result was the best that I was able to accomplish in attempting to crystallize the pigment.

Professor J. O. Reed has kindly examined this pigment with the spectroscope. For this purpose he employed a large Schmidt and Haensch spectrometer. An alcoholic solution of the pigment in a layer 10 mm. thick showed an absorption band in the deep red with its upper edge at 664. Absorption begins again in the red at 644, and extends to green at 526. There is slight transmission from 526 to upper blue at 455.

An alcoholic solution in a layer 5 mm. thick shows a dark band in the yellow at 578.8, with diffuse edges. Band extends from 651 in red to 546 in green. There is also a faint band in blue at 486, and there is absorption from 438 to end of violet.

The ether solution in a layer 10 mm. thick shows no distinct bands, but there is absorption in the green and the blue, beginning at 546 and extending to limit of violet. The same solution in a layer 5 mm. thick shows a faint band in blue at about 486.

From these studies I conclude that the pigment of the bacillus violaceus is a non-nitrogenous body, and at present I think it should be classified among the lipochromes. However, it must be admitted that this pigment differs in some particulars from the general description of lipochromes as given by Krukenberg and Zopf. Krukenberg states that under natural conditions lipochromes are usually found dissolved in fat. Concentrated sulphuric and nitric acids change them to a blue, green, or to an indigo blue. When examined with the spectroscope they may show two or even three absorption bands toward the violet end. They resist saponification and are soluble in chloroform, ether, alcohol, benzol, fat, and ethereal oils. They contain no nitrogen. The lipochrome obtained by Zopf from his bacterium egregium turns blue, then yellow, violet, red, and finally becomes colorless on treatment with concentrated sulphuric acid. Nitric acid has the same effect; concentrated hydrochloric acid acts very slowly, but finally decolorizes. It is soluble in alcohol, ether, methyl alcohol, chloroform, bonzol, and petroleum ether. It is insoluble in water. It shows two absorption bands: one at F, and the other, less distinct, between F and G.

The lipochrome reported by Halliburton is soluble in alcohol, ether, petroleum ether, benzol, chloroform, carbon bisulphid, and slightly in olive oil. It shows various shades of yellow in solution, except when dissolved in carbon bisulphid and chloroform, to which it imparts a pink coloration. Concentrated sulphuric acid turns it a dirty green, then bluish green, and finally brown. Concentrated nitric acid changes it to bluish green and then decolorizes. In concentrated alcoholic solution the spectrum shows the red absorbed to C and the blue end to E. In more dilute solutions less of the red end is absorbed, and the band is detached at F. Halliburton obtained this lipochrome from the blood of certain crustacea, and he named it tetronerythrin.

The effect of light upon lipochromes seems to be variable. According to Capranica, those lipochromes which are richest in fat are most resistant to the decolorizing influence of light. I have found that the pigment of the bacillus violaceus both in residue and in alcoholic solution is not altered by diffuse daylight, even after an exposure of more than four months. Even the purplish ether solution, which is easily changed to a yellow on heating, is not altered by exposure to diffuse sunlight.

This pigment dyes wool and silk excellently, and cotton fairly well. With wool and silk it forms a fast color, but cotton dyed with it is partially decolorized after frequent washing with hot water and soap. On silk this pigment brings out the glossy appearance and imparts a beautiful lavender color, which varies with the concentration of the dye solution.

The Pigment of the Bacillus Prodigiosus. This pigment was obtained by extracting the germ substance with alcohol. The alcoholic extract was filtered, evaporated on the water bath, and the residue re-extracted with alcohol. The portion insoluble in alcohol forms a brown pigment readily soluble in water. This is worthy of note, inasmuch as Bordoni-Uffreduzzi states that the red pigment of this germ is soluble in water, and the yellowish one soluble in alcohol. The pigment obtained by repeated solution in alcohol yields, when heated with potassium acid sulphate, acrolein. It is soluble in ethyl, methyl and amyl alcohol, chloroform and ether. It is insoluble in water, benzol, carbon bisulphid, and petroleum ether. It is soluble in acetic acid without any apparent change. When added to

an alcoholic solution, concentrated sulphuric acid does not change the color, but when added to the pigment sediment it turns it dark brown. Concentrated nitric acid turns the dried pigment light brown. Strong alkalies convert the pigment immediately to a brown. Oxidation with free chlorin decolorizes the alcoholic solution. When carefully reduced with nascent hydrogen, a colorless solution is obtained, but the original color may be restored by shaking with air or more quickly by careful oxidation with the yellow oxid of mercury.

Having discovered that carbon bisulphid, petroleum ether, and benzol do not dissolve this pigment, I determined to extract it with these substances in order to see if I could remove any or all of the fat. With this end in view I placed some of the pigment in a Soxhlet extractor and successively treated it with carbon bisulphid, benzol, and petroleum ether. Benzol and petroleum ether removed a small amount of a light yellow oil, which was found to be free from nitrogen, but the residue which remained after extraction with these solvents was found to contain a considerable amount of nitrogen. It also responded promptly to the acrolein test. It will be seen from this that I failed to remove the fat from the pigment by extraction with the above-mentioned solvents. My attempts to purify the pigment by saponification were quite as unsuccessful as those employed with the pigment of the bacillus violaceus.

Ultimate analyses of the pigment of the prodigiosus have been reported. Scheurlen made such an analysis, although he recognized the fact that he did not have his pigment in a chemically pure condition. He states that this pigment does not contain nitrogen, or, at most, only traces of this element. He made no attempt to determine the nitrogen in his ultimate analysis. Griffiths[15] reported the formula $C_{35}H_{56}NO_5$. However, ultimate analyses of substances known not to be chemically pure are absolutely worthless. The purest form of the pigment which I have been able to obtain contains nitrogen.

Professor Reed has examined this pigment for me with the following results: An alcoholic solution, 10 mm. thick, gives two distinct absorption bands. The first, which is well marked, lies in the green, with its center at 537, and its edges at 553 and 523. The second hand is found in the upper green at 514, with absorption continuing to the limit of the violet.

A concentrated alcoholic solution which had stood for six months

showed a heavy black band in the yellow green with its center at 572, and a second band of almost total absorption from lower edge in blue green at 520 to limit of violet. An old dilute alcoholic solution showed the first band in green, having its center at 544, and its edges at 562 and 527. The second band lies in the greenish blue, with center at 496 and lower edge at 510, with upper edge indistinct. In all the alcoholic solutions thus far examined, provided that they are not too dilute, two absorption bands appear, but the exact positions of these vary according to circumstances. Griffiths found that an alcoholic solution of this pigment gives two absorption bands, one in the blue and the other in the green. According to Krukenberg,[16] this pigment shows three absorption bands—one beyond D, the second immediately before E, and the third before F. Scheurlen states that the alcoholic solution of this pigment shows one absorption band which extends from E toward D, almost to the line 55. It will be seen from this that there must be some difference in the pigments studied by different investigators. However, I think I can reconcile some of these apparent discrepancies. There can be no question that Griffiths' observed spectra coincide with those from my alcoholic solutions. The statement of Scheurlen that there is only one band is explained by the fact that if the layer be reduced in thickness sufficiently only one absorption band appears. This is shown to be the case by the following experiments: An alcoholic solution of the pigment in a layer of 10 mm. thickness showed a characteristic black band in green, with the center at 546, a sharp lower edge at 555, and an upper diffuse edge ending at about 543; also, a faint band in the blue at 464. This same solution examined in a layer 5 mm. thick shows only one band with its center at 539.

The question of the identity of the pigment of the bacillus prodigiosus with fuchsin is an interesting one. This view is favored by Bordoni-Uffreduzzi, who reports several reactions in favor of his claim, but admits that in its behavior toward acids the pigment does not resemble fuchsin. Krukenberg denies the identity of the two, particularly on account of their spectra. According to him, the prodigiosus pigment furnishes three absorption bands, while fuchsin has only one, but, as we have already seen, this might be explained by variations in thickness of the layer. Schroeter[17] emphasizes the difference in behavior between the pigment and fuchsin toward acids, and Erd-

mann states that the pigment fades in twenty days to a dirty yellow, while fuchsin remains permanent. None of these investigators mention the occurrence of the pigment with a fat such as I have found. This combination suggests the possibility of this pigment being closely related to the lipochromes. However, it does not correspond with these substances in many of its reactions. Moreover, as already stated, I have so far been unable to obtain this pigment free from nitrogen. If this be done in the future it will probably be classed as a lipochrome, but until the pigment is obtained free from nitrogen it can hardly be placed among these bodies. So far as its similarity to or identity with fuchsin is concerned, I must refrain at present from the expression of any positive opinion.

The fact that this pigment readily dyes silk and wool was probably first observed by Erdmann, but has since been confirmed by Schroeter and Bordoni-Uffreduzzi. However, on this point there seems to be some difference between the pigment which I have used and that employed by the above-mentioned investigators. For instance, Erdmann and Schroeter found that fabrics dyed with this pigment became dirty yellow in about twenty days, while I have both silk and woollen articles dyed with the pigment of the prodigiosus which have been kept for six months, with only slight change in color. It is possible that the large amount of fat in which the pigment with which I have worked is dissolved has something to do with its greater stability. In this connection it should be stated that I have not used the pigment upon which I made the chemical tests for dyeing my fabrics, but in each case I took fresh cultures. Moreover, I adopted a slightly different method of removing the pigment, inasmuch as I found that this is necessary in order to get the most beautiful tints. Growths of the germ were removed by scraping the surface of the culture medium, and were then extracted with absolute alcohol and filtered. The articles to be dyed were first washed thoroughly with soap and water, then rinsed thoroughly in water, and placed in a beaker partially filled with distilled water. An alcoholic solution of the pigment was added until the desired color was secured, and the whole gradually heated to the boiling point. The fabrics were kept in this solution until properly dyed, after which they were removed and dried.

As has already been stated, when I was trying to purify the pigment for chemical examination I discovered that a brownish coloring

matter, soluble in water, but insoluble in alcohol, was obtained. The amount of this substance in proportion to the red pigment is small, and I believe it to be produced from the red pigment by some agent developed in the process of growth. The aqueous solution of this brownish pigment has a markedly acid reaction. The nature of the acid present and its relation to the pigment have not been studied. Aqueous solutions of this pigment give slight absorption in upper blue and violet, but there are no well-marked bands. An alcoholic solution of the red pigment when treated with ammonium hydrate changes to brown, the exact shade varying somewhat according to concentration. Spectroscopic examination of the pigment thus produced by the action of ammonia on the red coloring matter indicates that this substance is identical with the brown pigment which I found to be soluble in water. This brown pigment appears to be a much better dye and to be more resistant to light than either that of the violaceous or the red pigment of the prodigiosus. I have had an aqueous solution of this pigment standing in my desk for nearly six months, and there has been no apparent loss of color. It is possible that this pigment is preserved by the presence of the acid already referred to, and it may be that this acid is also an aid in the process of dyeing. In dyeing with this pigment it is only necessary to place the article in the aqueous solution and heat to boiling over a free flame, allowing the fabric to remain in the solution at the boiling-point until thoroughly colored. This pigment dyes cotton as well as silk and wool.

NOTE, August, 1902.—Prolonged exposure of fabrics dyed with these bacterial pigments cause them to fade quite perceptibly.

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PART III.—THE TOXICITY OF THE DRY, STERILE CELLS OF CERTAIN NON-PATHOGENIC BACTERIA.

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Micrococcus Prodigiosus. The organisms used in these experiments were the bacillus prodigiosus, bacillus violaceus, sarcina aurantiaca, and sarcina lutea. These organisms were grown on agar in Roux flasks and in the large tanks devised by Vaughan. After a period which varied in the different experiments, but averaged about fourteen days, the layer of germ substance was removed from the agar, repeatedly extracted with 96 per cent. alcohol, dried first between folds of blotting-paper, then in vacuo, and rubbed up into a fine powder in a mortar. The literature on this subject is not extensive. Steinhaus[1] injected sterilized cultures of the bacillus prodigiosus subcutaneously in cats, rabbits, and guinea-pigs, and found that suppuration resulted. On the other hand, Janowski[2] reached a contradictory result, inasmuch as he found that neither living nor sterilized cultures of the prodigiosus when injected subcutaneously in dogs and rabbits caused suppuration. I have not been able to find record of any experiments in which the toxicity of the cell of the prodigiosus has been tested. In fact, so far as I know, experiments with the dried, sterile substance of this organism have not been made.

Marx injected agar cultures of the bacillus prodigiosus in the thigh muscles of frogs. Inflammation was excited in from twelve to

twenty-four hours, and death resulted within twenty hours. From the dead bodies pure cultures were obtained, and with these white mice were inoculated, and died within twelve hours. However, the ordinary cultures of bacillus prodigiosus are not infectious to warm-blooded animals, and these experiments made by Marx do not concern our results, which were made with the germ substance.

TABLE I. *The Effects of Intraperitoneal Injections of the Air-dried Cells of the Bacillus Prodigiosus in Guinea-pigs.*

No.	Weight.	Dose in Mg.	Result.
1	260	50	Found dead within twelve hours.
2	305	50	" " "
3	265	50	" " "
4	320	50	" " "
5	305	50	" " "
6	287	20	" " "
7	272	10	" " "
8	260	5	" " "
9	252	1	Recovered.
10	367	5	"
11	270	3	Died within eighteen hours.
12	252	2	Recovered.
13	257	4	"

It will be seen from this table that the smallest fatal dose was 3 mg., which in this case made 1 part of the poison to 90,000 parts of the body weight. It will also be seen that several animals recovered from larger doses.

TABLE II. *The Effects of the Subcutaneous Injection of the Air-dried Cells of the Bacillus Prodigiosus in Guinea-pigs.*

No.	Weight.	Dose in Mg.	Result.
1	215	125	Died within twelve hours.
2	295	100	" "
3	245	75	" "
4	235	50	" "
5	380	30	Recovered.
6	350	20	"
7	245	10	"
8	235	5	"
9	237	4	"
10	325	3	"
11	242	2	"

It will be seen from this table that the minimum fatal dose when administered subcutaneously to a guinea-pig of from 200 to 300 grams weight is between 30 and 50 milligrams.

It should be stated that the lethal doses as indicated in the above tables apply only to the thoroughly washed germ substance. There is a large amount of mucilaginous material present in growths of the prodigiosus, and this is not washed out with alcohol. In order, therefore, to get the cell substance as pure as possible by physical agents, it should be washed thoroughly with water and subsequently with alcohol. When alcohol only is used the lethal dose will be found to be larger than is indicated in the above-given tables.

When a fatal dose of the germ substance is injected either intra-abdominally or subcutaneously in a guinea-pig there is immediate evidence of local pain. Often the animal cries out and runs about its cage, giving evidence of much suffering. It was at first supposed that this might be due to traces of acid, inasmuch as the bacterial cells were found in some instances at least to impart an acid reaction to water, but careful investigation showed that after every trace of acid had been removed from the cells the injections were still followed by indications of severe local pain. Indeed, it seemed that the more thoroughly the germ substance was washed the more acute was the pain induced by the injections. In all cases the local pain seemed to abate after from ten to fifteen minutes, and the animals became quiet. While no actual convulsions were seen in any of the animals, many of them appeared to be in a state of hyperesthesia, and the slightest touch caused marked twitchings. Unfortunately, all the animals died at night, and the symptoms immediately preceding and accompanying death have not been observed.

The following extracts from my protocol will show the postmortem findings when different sized doses were employed:

November 7, 1901, injected guinea-pig weighing 695 grams with 200 mg. of dried prodigiosus. (It should be stated that this material had not been thoroughly washed with water.) The pig died sometime during the night, and postmortem examination was made the next morning at 11. Masses of coagulated lymph were found between the lobes of the liver and on the under surface of that organ. Large quantities of the germ substance were also found under the liver and in the coils of the intestines. The adrenals were markedly congested.

The stomach was filled with food, the lungs were slightly congested, and cultures from the heart's blood remained sterile.

A guinea-pig weighing 260 grams received 5 mg. of the well-washed, air-dried germ substance at 4 P.M. It was found dead at 8 the next morning. Postmortem examination revealed the presence of about 10 c.c. of perfectly clear fluid in the peritoneal cavity. The mesenteric vessels were markedly congested, and the adrenals had a deep red color. The lungs showed a mottled, congested appearance. The spleen was of normal size, and all other organs seemed normal.

Guinea-pigs weighing 215 and 295 grams, and which had received respectively 125 and 100 mg. subcutaneously at 4 P.M., were found dead the next morning. Postmortem examination showed practically the same changes found in those that died from intraperitoneal injections. There was marked congestion of the mesenteric blood-vessels. The lungs were highly congested and the adrenals had a deep-red color. The heart was found to be in systole. The gall-bladder was greatly distended and filled with bile. A large amount of the injected germ substance was found under the skin at the point of injection. There was no pus. However, the mass of germ substance was surrounded by a clear gelatinous exudate.

By beginning with small doses a certain degree of immunity can be readily obtained with the dried germ substance of the prodigiosus. When administered at intervals of ten days it is usually safe to double or treble the dose at each injection. However, the process of immunizing guinea-pigs to the germ substance of the prodigiosus can be carried only to a certain stage, when apparently a very definite limit is reached. Beyond this point the animal rapidly emaciates and soon dies, apparently of inanition. From two pigs, which had been treated at intervals with three doses each, with respectively 3, 10, and 20 mg., blood serum was obtained, and with this the following observations were made: A serum from animals thus immunized, diluted with 10 volumes of distilled water, caused the organisms taken from a recent agar culture of the bacillus prodigiosus to agglutinate, while serum from normal guinea-pigs diluted in the same proportion had no effect. Prolonged observation, however, failed to show any evidence of bacteriolytic action on the part of this serum.

Some experiments were made, with the idea of determining whether or not the serum obtained from these guinea-pigs had any antitoxic

action against the dried germ substance. The result of these experiments convinces me that no marked antitoxic effect is possessed by this serum. Other experiments showed the absence of a specific precipitin in this serum.

BACILLUS VIOLACEUS. The cell substance of the bacillus violaceus was obtained in the same manner as that of the micrococcus prodigiosus. I have failed to find in literature anything concerning the toxin of this micro-organism. Experiments made after the manner already described give the results shown in the following table:

TABLE III. *The Effects of the Intraperitoneal Injection of the Air-dried Cells of the Bacillus Violaceus in Guinea-pigs.*

No.	Weight.	Dose in Mg.	Result.
1	220	30 . . .	Died in fifteen hours.
2	230	20 . . .	Died in less than twelve hours.
3	315	20 . . .	Recovered.
4	255	15 . . .	Died in sixty-five hours.
5	265	10 . . .	Died in less than twelve hours.
6	210	10 . . .	Recovered.
7	250	10 . . .	"
8	235	10 . . .	"

It will be seen from the above that the smallest fatal dose was 10 mg. administered to a pig weighing 265 grams, which is equivalent to 1 part of the poison to 26,500 parts of body weight. It will also be observed that the same thing happened in these experiments as in those with the cellular toxin of the prodigiosus—that is, that a number of animals recovered from the dose which killed one. It should be stated that when a weighed portion of the toxin was prepared for injection it was mixed with water and placed in a tube in the autoclave, and no attention was given to the time during which the substance remained exposed to heat. It is possible that this may in part at least account for the variable effects upon animals of like weights. This is a matter which must be investigated more carefully. No subcutaneous injections of this toxin were made.

The symptoms induced by the cellular toxin of the violaceus are practically the same as those observed after treatment with prodigiosus. The postmortem findings are indicated in the following extract from the protocol: "An examination of guinea-pig No. 5, as given in the above table, showed the presence of 10 c.c. of clear fluid in the ab-

dominal cavity. The adrenals were markedly hemorrhagic—this condition being much more marked than in animals poisoned with the toxin of the prodigiosus. All other organs seemed to be normal.

SARCINA AURANTIACA. A large amount of the cellular substance of the orange sarcine was obtained by the method already given, and thoroughly washed with both water and alcohol. The following table shows the degree of toxicity possessed by this germ substance:

TABLE IV. *The Effects of the Intraperitoneal Injection of the Air-dried Cells of the Sarcina Aurantiaca in Guinea-pigs.*

No.	Weight.	Dose in Mg.	Result.
1	245	25	Died within thirty-six hours.
2	400	20	Died within three days.
3	300	20	" "
4	420	15	Recovered.
5	365	15	"
6	210	15	"
7	235	15	"
8	255	10	Died within forty-eight hours.
9	305	10	Recovered.
10	295	10	"
11	280	10	"

It will be seen from the above that the smallest fatal dose of the cellular toxin of the sarcina aurantiaca is found to be 10 mg. in a pig weighing 255 grams, which is equivalent to 1 part of the poison to 25,500 of body weight. There is nothing in literature, so far as I can find, concerning the toxicity of the cellular substance of this organism.

Attempts were made to immunize guinea-pigs to this toxin, but it was found that even when the same dose was repeated the animal gradually emaciated and died. However, in a few instances some slight degree of immunity was secured, but even in these the animals often lost weight on repeating the injection when there was no increase in the size of the dose or when the increase was but trifling. From two pigs, each of which had withstood twice the minimum fatal dose, blood serum was obtained. The undiluted serum of these animals had a slight bacteriolytic action on recent cultures of the sarcine. After four hours of exposure I could see that some of the cells were gradually losing their highly refractive contour, and a few seemed to pass into solution. In one instance I allowed some of the serum

mixed with the sarcine to remain in a sealed hanging drop under the microscope over night. The next day I perceived that some of the cells had disappeared, inasmuch as the groups were both fewer in number and smaller in size. Moreover, here and there I could see shadows of the cells. Not having sufficient serum, I have not made plates in order to decide by differential count just how much bactericidal or bacteriolytic property the serum possessed. As in the case of the prodigiosus, I failed to find in the blood serum of these animals any indication of the presence of a specific precipitin. The blood serum obtained from these partially immunized animals apparently had slight antitoxic properties, as the following experiments will show: A guinea-pig weighing 370 grams was treated intraperitoneally with 100 mg. of the cell substance which had been mixed with 3 c.c. of sterile physiological salt solution, to which 10 drops of the serum was added. This animal remained unaffected by the treatment. A second guinea-pig, weighing 460 grams, was treated intraperitoneally with 150 mg. of the cell substance suspended in 3 c.c. of sterile physiologic salt solution to which 5 drops of the serum had been added. This pig died after forty-eight hours. Of course, these experiments are altogether too few in number to justify any positive conclusions one way or the other. However, they are of sufficient importance to lead to a repetition of this test, which undoubtedly will be carried out in this laboratory some time in the future.

One hundred and twenty-five milligrams of the germ substance mixed with water and injected into the abdominal cavity of a guinea-pig, weighing 250 grams, at 3.10 P.M., April 5th, caused death at 10.30 A.M., April 6th, and 200 mg. injected in the same way into a guinea-pig, weighing 335 grams, at 3.45 P.M., April 5th, caused death at 3 P.M., April 6th, and 225 milligrams injected into a guinea-pig, weighing 345 grams, at 3.55 P.M., April 5th, caused death at 2.30 P.M., April 6th.

SARCINA LUTEA. The germ substance of the lemon sarcine forms a light yellow powder, the individual cells of which are highly resistant both to heat and to chemical reagents.

It will be seen in Table V. that the smallest fatal dose in proportion to body weight was in No. 9. In this animal the proportion of the poison to body weight was 1 : 3850. However, in this case death did not occur until four days after injection. The smallest dose

which proved fatal within twenty-fours was in guinea-pig No. 4, in which the proportion of the poison to body weight was 1 : 2030.

TABLE V. *The Effects of Intraperitoneal Injection of the Air-dried Cells of the Sarcina Lutea in Guinea-pigs.*

No.	Weight.	Dose in Mg.	Result.
1	340	300	Died in seven and one-half hours.
2	180	128	Died in four and three-fourth hours.
3	405	200	Recovered after severe illness. (Six days after injection this animal weighed 95 grams less than at the time of treatment.)
4	180	88	Died in fourteen hours.
5	255	100	Recovered after severe illness.
6	257	125	Recovered.
7	385	150	"
8	390	150	"
9	385	100	Died four days after injection.
10	345	50	Recovered.
11	340	50	Died twelve days later from inanition.
12	365	50	Recovered.
13	262	25	"
14	232	25	"
15	375	20	"
16	392	10	"
17	287	5	"

Postmortem examination of the animals in the above list which died showed the presence, as a rule, of about 10 c.c. of clear fluid in the peritoneal cavity The lungs were slightly congested, but other organs seemed to be normal. Moreover, the congestion of the lungs was not constant.

It is worthy of note that germ cells taken from the peritoneal cavity with a hypodermic syringe eighty-nine hours after injection were all included in phagocytes, but even after this time such cells took the anilin dyes fairly well.

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PART IV.—THE CHEMISTRY OF SARCINA LUTEA.

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THE organism used in this investigation was grown upon Vaughan's incubating tanks, each of which offers twenty square feet of surface of culture medium. A good harvest yields about 50 grams of the dried germ, but we have not always been fortunate enough to obtain this amount with the lemon sarcine. Two methods have been resorted to for removing the growth from the surface of the agar. At first, the growth was moistened with alcohol and carefully detached from the subjacent medium, after which the germ substance was repeatedly extracted with alcohol, dried first between folds of blotting paper and then in vacuo, and pulverized in a mortar. This method gave a nice, clean powder to work with, but the alcohol so hardened the cells that they became very resistant to chemical reagents. It was found that when this method was employed the germs, after two extractions in the cold with 0.5 per cent. potassium hydrate and one extraction with 5 per cent. potassium hydrate at ordinary temperature, and then autoclaving with 5 per cent. alkali at 120°, for thirty minutes, still took the anilin stains perfectly, and under the microscope appeared to be unaltered. This indicated that the alcohol had very seriously hardened the cells. For this reason we tried another method, which consisted in moistening the germ growth in the tank with water and then detaching it from the agar. In some instances the germ substance, without the addition of water or any other liquid, has been scraped from the agar and subsequently washed with water. When either of these methods was practised the germ mass was repeatedly extracted with water, collected upon a filter-paper, washed, dried between folds of blotting-paper and subsequently in vacuo, and then pulverized. In still other instances, especially when the growth in the tank contained considerable water, this was scraped off, and,

after the addition of acid to the aqueous suspension, extraction was begun at once.

Inasmuch as most of my work has been done with either alkaline or acid extracts of the germ substance, it will be well to discuss the subject under two heads. The alkaline extracts were examined for proteids, nucleoproteids, nuclein, nucleic acid, carbohydrate, and basic substances, while the acid extracts were tested especially for protamin, hexon, and xanthin bases, and the residue for cellulose.

ALKALINE EXTRACTS. At first I attempted to extract the germ substance which had been treated with alcohol by shaking it in the cold with 0.5 per cent. potassium hydrate, but inasmuch as no appreciable amount of substance was removed in this way, the strength of the alkali was increased to 5 per cent., but as long as the extraction was carried out at ordinary temperature no better results were obtained. After meeting with these failures I autoclaved the germ substance, first with 5 per cent. and then with 10 per cent. alkali. The extracts thus obtained were thick, syrupy liquids of a dark-brown color, and contained a deposit of a slimy, mucilaginous substance. This made filtration very difficult. Filtration through porcelain, even with the aid of a powerful pump, was a complete failure, because of the slowness with which the fluid passed through. Suction through cloth or paper proved ineffective. The most satisfactory method tried was that of using several thicknesses of hardened paper without the pump.

All the alkaline extracts gave the xanthoproteic and biuret tests, but did not respond to Millon's reagent. The presence of a carbohydrate was indicated by the formation of the furfurol ring with α-naphthol and sulphuric acid.

A brief statement of the details of the method employed will here be given. Twenty grams of germ substance was autoclaved with 25 parts (500 c.c.) of 10 per cent. potassium hydrate at 120°, first for thirty minutes and then for an hour. At the end of this time there remained a considerable residue which no longer gave the proteid reactions, but did respond to the carbohydrate tests with α-naphthol, although it did not reduce Fehling solution, even after it had been boiled for some time with dilute hydrochloric acid. Cellulose could not be detected by any of the tests employed. Schweitzer's reagent failed to dissolve the residue, and it gave no color with iodin, even after treatment with concentrated sulphuric acid. A portion

was dried and heated with soda lime, when it evolved a gas which turned red litmus-blue, thus indicating the presence of nitrogen which had been reduced to ammonia. The odor of burning feathers also indicated the presence of nitrogen. From these experiments I conclude that the residue left after extraction with 10 per cent. potassium hydrate at 120° contains a carbohydrate, but there is nothing to indicate that it is cellulose. Other investigators, working with different bacteria, have been left somewhat in doubt concerning the existence of cellulose. Nishimura[1] reports the finding of cellulose in the tubercle bacillus twice, and failure to find it in four attempts. Even in the two instances in which he thought that he found this substance he states that it was present in very small amount, and he concludes that cellulose is not a constituent of the tubercle bacillus, of the prodigiosus, of the staphylococcus, and of a water bacillus which he examined; but that there is present in these cells a carbohydrate which can be brought into solution by boiling with 2 per cent. sulphuric acid, and which by this means can be changed to a reducing sugar. De Schweinitz and Dorset[2] decided from their investigations that cellulose is present in the tubercle bacillus, but only in minute amount, and that it is not found in the bacillus of glanders. Vincenzi[3] states that the bacillus subtilis contains no cellulose, and that the form-giving substance in this organism is a nitrogen-containing body.

The soluble portion of the alkaline extract after filtration through paper was acidified with hydrochloric acid and treated with three volumes of 95 per cent. alcohol, which produced an abundant white, curdy, sticky precipitate. Precipitation by means of alcohol with acetic and picric acids was also tried, but did not prove so satisfactory. I attempted to purify this substance by repeated solution in alkali and reprecipitation with acidified alcohol, but I found that each time the quantity was diminished, and it became evident that a large proportion of it remained dissolved in the alcohol. After filtering, washing, and drying in an atmosphere of carbon dioxide, the powder finally obtained weighed only 0.7872 g. It contained phosphorus and responded to the carbohydrate test, but not to the proteid reactions. Its phosphorus content was determined quantitatively, and was found to be .861 per cent., which is too low to indicate the presence of nucleic acid or nuclein in anything like a pure condition. However, as I have already stated, this precipitate consisted in part of carbo-

hydrate, and this undoubtedly accounts for the small percentage of phosphorus. Possibly the substance consisted largely of nucleoproteid, the percentage of phosphorus in which varies, according to other investigators, from 0.5 per cent. to 1.6 per cent. Galeotti[4] found in bacillus ranicideus a nucleoproteid with a phosphorus content of from 1.1 per cent. to 1.8 per cent. The amount of material obtained in my investigation was not sufficient to enable me to investigate this matter further. Ruppel[5] reports in bacillus tuberculosis nucleic acid, both free and combined. Levene[6] also thinks he has obtained it from the bacillus tuberculosis, and Blandini[7] isolated a nuclein and a nucleoproteid from cultures of the typhoid bacillus. Lustig and Galeotti[8] obtained from the pest bacillus a substance which they believed to be a nucleoproteid.

From the first alcoholic filtrate after removal of the precipitate above referred to, and after neutralization and concentration in vacuo at from 22° to 42°, I obtained a precipitate with hydrochloric acid. This precipitate was soluble in excess of acid and was partly organic, but it contained a small percentage (0.038 per cent.) of inorganic phosphorus, also an undetermined amount of magnesium.

The remaining filtrates were concentrated in vacuo at from 23° to 45° without neutralization. On treatment with ammonia, these yielded a dark-brown precipitate which proved to be soluble in hydrochloric acid, from which it was reprecipitated on the addition of ammonia. The behavior of this substance suggested its basic character, but the amount obtained was insufficient for positive identification.

Acid Extracts. The acid extracts were made with 1 per cent. sulphuric acid, first by volume, afterward by weight. The germ substance was heated with the dilute acid on the water bath for from three to five hours, and the insoluble residue was subsequently extracted for the same length of time and at the same temperature with 2 per cent. potassium hydrate. I was unable to precipitate protamin from the acid extract with alcohol, but after first neutralizing with sodium hydrate a voluminous precipitate was obtained with alcohol. This precipitate contained a large amount of sodium sulphate, but by careful treatment with a calculated quantity of barium chlorid before neutralization and before the addition of the alcohol, I was able to get rid of a large part of the sulphuric acid. This pre-

cipitate proved to be a carbohydrate, which reduced Fehling's solution after being boiled with dilute mineral acid.

In the alcoholic filtrate from the portion soluble in water, after evaporation in vacuo, I likewise obtained a carbohydrate which reduced Fehling's solution after being boiled with dilute acid. The other portion of the concentrated filtrate soluble in alcohol was precipitated with platinum chlorid, and the amount of platinum in the compound determined quantitatively. It was found to be 37.63 per cent.

In the alkaline extracts made from the residue after treatment with dilute acid I obtained by precipitation with hydrochloric acid a substance which gave the furfurol ring, but which did not reduce Fehling's solution after being boiled with dilute acids. This substance was found to contain nitrogen, inasmuch as Berlin blue was obtained after reducing it to a cyanid with metallic sodium. The filtrate from this precipitate showed the biuret, xanthoproteic and carbohydrate tests. It was precipitated with five volumes of absolute alcohol, and this precipitate showed the presence of a carbohydrate and inorganic phosphorus.

The acid extracts give only the xanthoproteic reaction among the proteid color tests, but I am inclined to the opinion from the proteid reactions obtained at various stages, from the phosphorus present, and from the carbohydrate found, that it is quite probable that this organism consists largely of a glyconucleoproteid.

Others have found carbohydrates present in bacteria. Levene[6] obtained a glycocin-like body from the tubercle bacillus, and he believes this substance to be present in combination, because while he could isolate it only in small quantities from sodium chlorid or ammonium chlorid extracts, he obtained it in larger amounts in the residue after such extraction. Bendix[9] tells of a pentose found in tubercle bacilli. Proteid bodies have been found in anthrax by Nencki,[10] in the pneumococcus by Brieger, and in the tubercle bacillus by Hammerschlag[11] and by Weyl.[12] Ruppel[5] found a protamin in the tubercle bacillus.

Protamins have been regarded as the simplest group of proteids. The first known member of the group was isolated in 1874 by Miescher,[13] who at the same time isolated nucleic acid. During the same year Miescher's work was extended through the investigation of Piccard,[14] after which the work along this line stopped until Kossel

took it up in 1894 On cleavage the protamins yield the hexon bases, lysin, arginin, and histidin. They differ from more complex proteids, inasmuch as they do not contain the amido group. Protamins have been found in the mature spermatozoa of fish (Kossel,[13] Kurajeff,[15 17] Morkowin[16]), but not in the spermatozoa of higher animals (Matthews[18]).

Miescher's method consisted in extracting the spermatozoa with dilute hydrochloric acid and precipitating the protamin from the neutralized extract with platinum chlorid, after which the platinum was removed with hydrogen sulphid. Purification was secured by repeated precipitations with platinum. Kossel's[13 19] method consisted in shaking the finely divided material with water, straining through gauze, precipitating the milky fluid by the careful addition of acetic acid, boiling the spermatozoa with alcohol, extracting with ether, then drying, and subsequently extracting the dried cells with 1 per cent. sulphuric acid, shaking for fifteen minutes and repeating the extraction six times. The acid filtrates are then precipitated with three volumes of alcohol, and the precipitate thus obtained is purified by solution in hot water and reprecipitation with alcohol. The protamins contain 30 per cent. or more of nitrogen, and are basic in character. The salts which they form with mineral acids are soluble in water, but insoluble in alcohol and ether. They are more or less readily precipitated with neutral salts, such as sodium chlorid. Among the salts of the protamins the sulphate, picrate, and double platinum chlorid are the most important, and are used in its preparation. The protamins are levogyrate. They give the biuret test, but not Millon's reaction. Their salts are precipitated in neutral or faintly alkaline solution by tungstic, picric, chromic acids, and alkaline ferrocyanides. (Hammersten,[20] Vaughan and Novy.[21])

Thinking that possibly the treatment to which the sarcine cells had been subjected had been vigorous enough to break up proteid or protamin bodies that might be present, I made determinations of nitrogen by the Kjeldhal method in three different portions: (1) in the acid extract itself; (2) in the alkaline extract of the residue from the acid extract, and (3) in the final residue. The following results were obtained: Acid extract contained 0.55 mg. of N per c.c.; alkaline extract contained 0.7 mg. of N per c.c.; final residue contained 2.1 mg. of N per c.c.

I now began to look for hexon and xanthin bases. So far as I know, hexon bases have never been obtained among the decomposition products of bacterial cells. So far as the xanthin bases are concerned, Nishimura[22] found 0.17 per cent. of xanthin, 0.08 per cent. of adenin, and 0.14 per cent. of guanin in his water bacillus. It has been suggested that in Nishimura's experiments these bases might have come from the potato upon which his organism was grown, but inasmuch as the potato contains only a very small percentage of proteid, this is not likely. Lustig and Galeotti[3] report guanin obtained from the pest bacillus, and Galeotti[4] says that a nucleoproteid separated from the bacillus ranicidus yielded xanthin bases, although the percentage of nitrogen was low.

I have gone through the process of testing for xanthin bases four times. Three times the acid extracts were carefully precipitated with powdered silver nitrate crystals until a drop of the solution gave a yellow instead of a white precipitate with barium hydrate. The precipitate was filtered out, washed, dried, and then worked up for xanthin bases. The fourth time the process was almost the same, the difference being that 33⅓ per cent. acid extract had been made. This was first almost neutralized with barium hydrate, the barium sulphate filtered out, carefully washed out and boiled with water, and the still slightly acid extract was precipitated with silver sulphate instead of silver nitrate. The first silver nitrate precipitate was investigated according to the method given by Krüger and Salomon;[23] as no satisfactory separation was thereby obtained, the last three precipitates were separated according to the method of Kossel and his pupils, as outlined by Hammersten,[24] for the separation of the four bases, xanthin, hypoxanthin, guanin, and adenin. The precipitate was dissolved as completely as possible in boiling nitric acid (sp. gr. 1.1), a little urea having been added to prevent nitrification, filtered hot, concentrated somewhat, and allowed to cool. On cooling, only a slight residue of the guanin-hypoxanthin-adenin portion separated out. On decomposing this precipitate, treating with ammonia, and evaporating, the amount obtained was so small that it was not possible to make separation of the bases, but ammoniacal solution produced a comparatively heavy flocculent organic precipitate. The nitric acid filtrate containing the xanthin portion was precipitated with ammonia. A heavy, reddish-brown, mucilaginous precipitate came down, but was

not sufficient in quantity or sufficiently free from impurities to justify an ultimate analysis.

The filtrates from the silver precipitates worked up for xanthin bases were tested for the hexon bases, histidin, arginin, and lysin, according to the method given by Kossel.[25] The filtrate was saturated with powdered barium hydrate at 40° and filtered. The precipitate was rubbed up with baryta water, filtered, and washed thoroughly with water containing barium hydrate. This precipitate was examined for histidin and arginin, and the filtrate for lysin. No attempt has been made as yet to test for the presence of the amido acids. I have repeated the tests for the hexon bases five different times, and each time the results for histidin and arginin have been negative. As to the lysin, in all five attempts where lysin picrate should be formed I have obtained a yellow, thick, oily body, which, however, could not be crystallized. This oily body was shaken up with ether to remove excess of picric acid, but when I attempted to purify it by redissolving it in alcohol it was no longer completely soluble, inasmuch as a part of it hardened into a solid which seemed somewhat crystalline, and the remainder was precipitated by alcohol. However, it was found to be readily soluble in water, especially in hot water, and although no crystals were obtained on concentration of the aqueous solution, the same heavy oil separated. In order to obtain the hydrochlorid, if possible, the oily substance was treated with hydrochloric acid in a little water and the picric acid shaken out with ether. From the solution on concentration an imperfectly crystalline mass was obtained. It will be necessary for me to obtain more material before I can absolutely identify this substance with lysin. It may be that I have not lysin, but there is undoubtedly present some organic body which, in its chemical behavior at least, is very similar to lysin.

In conclusion, I may state that my work has resulted in showing that the cells of sarcina lutea contain at least two carbohydrates, some substance yielding xanthin or similar bodies, and some other substance yielding lysin or a closely related substance. The carbohydrates differ from one another in the fact that one is converted into a reducing sugar when boiled with acid, while the other is not. The second carbohydrate is evidently closely combined with some nitrogenous body, as is shown by the difficulty which I have had in freeing it from

nitrogen. The xanthin-like bases undoubtedly come from some nuclein body, the presence of which is still further indicated by the amount of phosphorus in the germ substance. The lysin-like substance indicates the existence in the cell of a proteid body. From this research I feel justified in concluding that the cell of sarcina lutea is made up largely of a glyconucleoproteid.

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PART V.—THE CHEMISTRY OF THE BACILLUS COLI COMMUNIS.

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INTRODUCTION. A study of the chemistry of bacteria includes the investigation of both intracellular and extracellular products. The constituents of the cell itself are of interest, both to the bacteriologist and to the physiologic chemist. Among the extracellular products of bacterial activity we may consider the cell excretions and the substances formed by the cleavage action of the cell or its enzymes on the constituents of the culture medium. A knowledge of the chemistry of bacteria should throw light not only upon their pathogenic and toxicogenic action, but also upon the problems of immunity and healing. Some years ago Petruschky[1] called attention to the value of chemical investigations in bacteriology, saying that the problem of immunity seems to be passing more and more into the domain of chemistry, and that the vital points are to be sought in the finer relations between bacterial chemistry and biochemistry. Leeds[2] speaks of the chemical operations which lie at the foundation of bacteriologic work, and predicts that the advances to be made in the near future are to be looked for mainly on the chemical side. Macfadyen and Rowland[3] state that the great aim of biologic inquiry at the present time is to obtain a more intimate knowledge of vital processes. These processes, whether normal or morbid, are in their essence intracellular. The striking resemblance between all young cells, whether plant or animal, has long been recognized. It is only after they are differentiated for various functions that they assume their infinite variety. The typical structure for the young cell consists of membrane, protoplasm, and nucleus. According to Neumeister[4] the primary constituents found in every living, growing cell, and taking part in its vital processes, are the essential components of protoplasm and nucleus. These include albumin, globulin, nuclein, and

neucleinic acid. The mineral constituents, such as phosphates of potassium, calcium, and magnesium, and certain organic compounds of phosphorus and iron, must, according to Neumeister, be included.

The microscopic study of bacteria suggests that these cells are more homogeneous than most others. Whether or not the bacterial cell contains a nucleus is a matter of discussion. Migula claims that there is no nucleus; Bütschli, that the main body of the cell, that which is readily stained, is all nucleus; and Babes and Ernst claim that there are many small nuclei. These differences of opinion indicate that the structure of the bacterial cell is quite different from that of the typical one. A similar conclusion may be drawn from the diversity of opinions in regard to the existence of a cell membrane: ranging from the theory that it has a silicious skeleton, according to Hallier,[5] to Migula's[6] suggestion that it is the outer layer of protoplasm, and that instead of playing a passive rôle, as does the cellulose wall in higher plant cells, it takes an active part in the vital processes.

Does this divergence from the typical cellular structure imply corresponding divergence in chemical composition? Shall we find nuclein whether the cells contain nuclei or not? Are the proteids and nucleins such as are found elsewhere? If protomins are the simplest of the proteids, as Kossel believes, we should find them or their decomposition products, the hexon bases. Possibly there is still a simpler form of proteid to be found in these structures.

In the absence of data in regard to the composition of the colon bacillus, it is interesting to note what is known of other bacteria, bearing in mind, however, that it is not safe to assume that whatever has been ascertained concerning the composition of one species is true of another. Nencki thinks there are greater differences in the chemical composition of nearly related forms among bacteria than among other orders of either plants or animals, and Hammerschlag calls attention to the varying amounts of nitrogen as showing that the relative proportions of proteid and nitrogen free substance in bacteria are subject to great variation.

Bacterial Proteids. In 1879, Nencki and Schaffer[7] separated a proted from a mixed culture of putrefying bacteria. To this they gave the name mykoprotein. The germs were dried, first on the water bath, and then in an oven at 110° to constant weight, pulver-

ized, and extracted with alcohol and ether. The residue thus obtained was digested on the water bath with 0.5 per cent. potassium hydrate. From these alkaline extracts mykoprotein was precipitated by neutralization and saturation with sodium chlorid.

Mykoprotein contains 52.32 per cent. C, 7.55 per cent. H., 14.75 per cent. N, and neither sulphur nor phosphorus. It forms amorphous flakes, soluble in water when freshly precipitated, but after drying at 100° it is no longer completely soluble. The aqueous solution is acid in reaction and is not precipitated by alcohol, but is precipitated by picric acid and other alkaloidal reagents. It gives Millon's and the biuret test, but not the xanthoproteic. On being fused with potassium hydrate it yields ammonia, amylamin, phenol, valerianic acid, leucin, and traces of indol and skatol.[7a]

A few years later Nencki[8] attempted to prepare mykoprotein from cultures of anthrax. To his surprise he found only traces of this substance in anthrax spores, but obtained a new body, which he called anthrax protein, which differed in composition and properties from mykoprotein. Anthrax protein is closely related to plant casein and animal mucin. It is easily soluble in alkalies, insoluble in water, acetic and dilute mineral acids. From alkaline solution it is precipitated in white flakes by acids. Since both anthrax protein and mykoprotein contain no sulphur, Nencki concludes that this is not a necessary constituent of living protoplasmic proteid. Dyrmont[9] made an analysis of anthrax protein with the following results: C, 52.1 per cent.; H, 6.82 per cent.; N, 16.2 per cent. and a trace of ash.

Brieger[10] found in Friedlander's pneumococcus a proteid substance that contained less nitrogen than is found in mykoprotein. This body is partially soluble in water, and is precipitated on boiling, but redissolves on acidulation with dilute nitric acid.

Lewith[11] reports work done by Hellmich upon a hay bacillus grown on synthetic medium. The bacterial cells in this case were extracted with neutral salts at ordinary temperature and a globulin, coagulable by heat, was obtained. Subsequent extraction with dilute alkali gave another coagulable substance described as an albuminate, and said to resemble casein.

Buchner's[11a] experiment seemed to prove that the intracellular contents of certain bacteria are pyogenetic. This investigator extracted

a proteid from many species of bacteria with dilute alkalies, and precipitated the alkaline solution with dilute acids. The amount of soluble proteid obtained in this way varied greatly, according to the species of bacteria employed. Bacillus pyocyaneus yielded the best results, 19.3 per cent. of the dry substance being precipitated from the alkaline extract. By another method the same investigator obtained proteids which are soluble in water and are not precipitated by dilute acids. He believes these to be nearer the proteid of the living cell. The bacteria were spread out in thin layers, dried for several days at 38°, rubbed up with water, boiled on the sand bath with a reflux condenser or heated in the autoclave at 120°, filtered through sand, and precipitated with absolute alcohol. In this way Buchner succeeded in extracting more than half the weight of the bacteria.

Brieger and Fraenkel,[12] Prosskauer and Wassermann,[13] and Dzierzgowski and Rekowski,[14] all obtained so-called toxalbumins from diphtheria cultures and made ultimate analyses of the same, but inasmuch as subsequent investigations have shown that these bodies were by no means pure, it is unnecessary to give their results.

From the bacillus tuberculosis Hammerschlag[15] extracted with dilute alkali a proteid which can be precipitated with ammonium sulphate. Buchner[16] extracted the same germ with from 40 to 50 per cent. of glycerin, and thus obtained what he believed to be the active principle of tuberculin. Hoffman[17] reports the isolation of six proteids from the tubercle bacillus, but inasmuch as he describes no attempt at purification, it is likely that they are not all distinct. Weyl[18] believed that he had separated the membrane from the protoplasmic contents of the cell, and from the latter he isolated a body which he classed as a toxomucin. The most important work on the chemistry of the tubercle bacillus is that of Ruppel.[19] Bouillon cultures were filtered through porcelain and the germ substance thus obtained was dried, pulverized, and extracted with water. The aqueous extract was precipitated with acetic acid, and the proteid thus obtained treated with dilute sulphuric acid, which extracted protamin sulphate. From this the free base was isolated, to which the name tuberculosamin was given.

Nuclein and Related Compounds. Vandervelde[20] reports finding nuclein in bacillus subtilis, and Dreyfuss[21] believes it to be

present in all bacteria. This belief is founded upon the behavior of bacteria toward basic anilin dyes. Gottstein[22] finds that various bacteria, including the colon bacillus, decompose hydrogen peroxide both during life and after death. He concludes from this, from the presence of phosphorus, and from the affinity of bacteria for basic anilin dyes, that they contain nuclein. Nishimura[23] obtained nuclein bases from cultures of a water bacillus grown on potato. The germ substance was removed, extracted with alcohol and ether, then repeatedly extracted with 0.15 per cent. sulphuric acid, boiling with reflux condenser, heating in the autoclave at 105°, and further at ordinary temperature. From these acid extracts xanthin silver, adenin picrate, and free guanin were isolated in amounts of 0.17 per cent. xanthin, 0.08 per cent. adenin, and 0.14 per cent. guanin. Lustig and Galeotti[24] obtained a nucleoproteid from alkaline extracts of the pest bacillus, and pepton and guanin were found after digestion with pepsin. From the effect of methylene blue on this germ and its appearance under the microscope after extraction, they infer that the alkali removes nuclein without destroying the cell membrane. Galeotti[25] extracted an organism similar to bacillus ranicidus with 1 per cent. potassium hydrate, and obtained a substance containing from 11.99 to 12.21 per cent. of nitrogen, and from 0.94 to 1.16 per cent of phosphorus. From its reactions and its composition he pronounced this substance a nucleoproteid. After several precipitations partial decomposition seems to take place as the proportion of phosphorus becomes higher. By further decomposition true nuclein was obtained. Aronson[26] extracted diphtheria germs with from one-fifth to one-tenth normal alkali in the cold, at 100° and 130°. He precipitated these extracts, first with acetic acid and then with acidulated alcohol, sometimes with alcohol to which ether and a little acetic acid had been added. The precipitate with acid is a white powder giving the biuret, xanthoproteic, and the Adamkiewicz test. Among its decomposition products are xanthin bases, pentose and albumin, thus proving the presence of nucleoproteid. By adding acid alcohol to the acid filtrate a new precipitate is obtained which, after purification, yields nucleic acid. Xanthin bases, pentose and phosphate, were obtained from this precipitate. Blandini[27] reports a nuclein and a nucleoalbumin obtained from cultures of the typhoid bacillus. Klebs[28] found evidence that nuclein makes up the larger part of the tubercle bacillus. He

extracted with ether and benzol, and digested with pepsin and hydrochloric acid, then dissolved the residue in alkali. From the alkaline extract after repeated precipitation with alcohol, he obtained a nuclein containing from 8 to 9 per cent. of phosphorus. Hahn[29] rubbed up moist tubercle germ with sand, treated the mixture with water, 20 per cent. glycerin, or physiological salt solution, reducing it to the consistency of a dough, and subjected this to gradually increasing pressure of from 400 to 500 atmospheres. The clear expressed liquid contained a large amount of coagulable proteid. This substance decomposes hydrogen peroxid, but loses this property on being heated. It gives the various proteid reactions and behaves like a nucleoalbumin. Ruppel[19] obtained a nucleic acid with 9.42 per cent. phosphorus from the residue left after preparing the tuberculosamin previously mentioned. This acid, which he named tuberculinic acid, is partly combined with tuberculosamin and in part is free. Levene[30] obtained three proteids from tubercle germs grown on media containing no proteid. The dried germs were ground for two to three days in a porcelain mill, then extracted repeatedly for two days with 8 per cent. solution of ammonium chlorid. These proteids coagulate at from 50° to 64°, 72° to 75°, and 94° to 95°, respectively. Ammonium sulphate precipitates all of them; sodium chlorid only the first; 50 per cent. magnesium sulphate the first; magnesium sulphate to saturation the second but not the third. It requires less acid to precipitate the first, but 0.2 per cent. hydrochloric acid precipitates all three. The third is richer in phosphorus than the others. Levene states that the tubercle bacillus contains chiefly nucleoproteids. One of these differs from the others in that it is not precipitated by magnesium sulphate and does not give the biuret reaction. It contains nuclein. He calls attention to the coincidence between the temperature point of coagulation of the first proteid and that necessary for the sterilization of the bacillus. He believes that tuberculin is a specific substance having the nature of a nucleoproteid. The same investigator made a study of tuberculinic acid. He found little free acid in mannite synthetic medium cultures, but considerable in beef-broth cultures. Different samples differ in composition and some experiments suggest that tuberculinic acid is less stable than any other known nucleic acid. According to De Schweinitz[31] a nucleo-albumin present in the tubercle bacillus appears to be the fever-producing

principle of this organism. Maragliano[32] digested the tubercle germ on the water bath with water. The aqueous extract thus obtained was evaporated to dryness and the residue found to be toxic.

CARBOHYDRATES. One of the earliest investigations upon the composition of bacteria was that of Scheibler[33] upon leuconostoc mesenteroides. The viscous growth of this germ in beet juice, after extraction with alcohol, was boiled with milk of lime. From the filtrate a gum was obtained which the author regards as an anhydride of dextrose, since by slow hydrolysis it is converted into the latter. To this substance he gives the name dextran. It is white, amorphous, soluble in water, dextrorotatory, having three times the rotary power of cane-sugar. Analysis corresponds closely to the formula $C_6H_{10}O_5$. Scheibler states that this germ contains ash, fat, water, dextrin and a substance containing phosphorus and nitrogen, which he believes to be protagon, or something closely resembling it. Kramer[34] separated from the slime of bacillus viscosus sacchari two modifications of a carbohydrate of the formula $C_6H_{10}O_5$. Both were optically active, and on being boiled with dilute acid reduced Fehling's solution. Ward and Green[35] studied a species of bacterium from Madagascar sugar-cane and found that it secretes invertase. In sugar solutions it produces a viscous growth which gives an opalescent solution with water. This aqueous solution when treated with alcohol yields a bulky, flocculent precipitate, which was found to contain two carbohydrates, one of which gives an osazone and is optically active, while the other is inactive. They regard these bodies as related to, but not identical with, Scheibler's dextran, and are not certain whether they are products of the vital processes of the organism or are cleavage products. Vincenzi[36] failed to find any evidence of cellulose in bacillus subtilis. However, Dreyfuss[21] heated masses of the same germ to 180° with concentrated alkali, and from this extract he obtained a substance which reduces Fehling's solution and from which he prepared glucosazone crystals. He concluded that cellulose is present. However, this conclusion is questionable. He obtained like results from pyogenic bacilli. Hammerschlag[15] concludes that the tubercle bacillus contains cellulose. The material used had been previously extracted with alcohol, ether, and 1 per cent. potassium hydrate. A portion was dissolved in concentrated sulphuric acid, diluted and boiled, after which it reduced

Fehling's solution. Another portion was treated with potassium chlorate and nitric acid, but most of the substance remained undissolved. A third portion partly dissolved in ammoniacal copper solution. Hammerschlag states that if one assumes that the nitrogenous material in the tubercle bacillus is all proteid, and that the proteid contains 16 per cent. of nitrogen, this germ contains 36.9 per cent. of proteid, 28.1 per cent. of cellulose, 27 per cent. of substance soluble in alcohol, and 8 per cent. of ash. Hemicellulose was found by Nishimura[23] in a water bacillus, in prodigiosus, and in staphylococcus pyogenes. De Schweinitz and Dorset[31a] extracted dried tubercle bacilli with alcohol, digested the residue with 1.25 per cent. sodium hydrate for from forty to sixty minutes, washed the residue, then digested with 1.25 per cent. sulphuric acid, then washed, dried, and ignited. The loss by ignition should give cellulose. Accordingly they report 6.95 per cent. cellulose in the tubercle bacillus, and 5.87 per cent. in the glanders bacillus. However, in the same article these authors state that cellulose is probably present in small amount in tubercle bacillus, but not found in the bacillus of glanders. Brown[37] boiled the "membrane" of bacterium xylinum twenty minutes with 10 per cent. potassium hydrate. This digested the bacteria, but left the film apparently unchanged. The residue was washed with dilute hydrochloric acid, then with water, and treated with bromin according to Müller's method for obtaining cellulose. The product obtained seems to be identical with that from cotton, dissolving in ammoniacal copper solution and in strong sulphuric acid. Moreover, it gives a reducing sugar which is dextrorotatory, even from cultures grown on media containing only levorotatory substances. Analysis shows a close agreement with that of cellulose, and Brown regards this as cellulose proper, differing from the metacellulose usually found in yeast and other fungi. He found no trace of dextran. He regards the formation of cellulose as a process of assimilation and not of fermentation. Bendix[37a] extracted dried germs with 5 per cent. hydrochloric acid over the free flame; cooled, made alkaline, then acidulated with acetic acid in order to precipitate the proteid. The filtrate gave with phenyl hydrazin an osazone which, when purified, melted at 153° to 155°, thus showing it to be pentosazone. This substance gave the orcin and optical tests for pentose. He obtained pentose from

diphtheria and tubercle bacilli, and also from a mixed culture of fecal bacteria, but not from the typhoid bacillus. He found this pentose combined with a nucleoproteid. Aronson[36] found pentose with nucleoproteid in the alkaline extracts of diphtheria bacilli. He says that the residue after complete extraction with alkali contains carbohydrate, which is neither cellulose nor chitin. It is dextro-rotary and gives an osazone.

Meyer[38] thinks that in some species of bacteria fat is stored up, while in others complex carbohydrates take their place. One species growing on barley gives a substance colored blue by iodin, and easily soluble in malt diastase, and in saliva. Bacillus subtilis gives a compound which is colored red by iodin and is dissolved by saliva and by boiling with dilute sulphuric acid. The author is uncertain whether this is glycogen or amylodextrin. A mixture of the carbohydrates obtained by this investigator acts like a mixture of much amylodextrin and a little β-amylose. As found in the cell it is easily soluble in water.

Levene[30] obtained a glycogen-like body from the tubercle bacillus. He extracted the germ substance with salts, or better with alkali, and removed the proteid by picric and acetic acids; then by addition of alcohol, glycogen and nucleic acid were precipitated together and were separated by means of copper chlorid. This glycogen is soluble in water, gives the iodin color test, does not reduce Fehling's solution, but does so after being heated with mineral acids. Chitin, or a related substance, was found by Emmerling[39] in the zooglea of bacterium xylinum. From 110 grams of moist impure material he obtained 0.2 grams of crystals of glucosamin hydrochlorid. Helbing[40] believes that chitin makes up a large part of the tubercle bacillus, and states that this is the cause of the peculiar staining properties of this organism. The experimental proof of the first premise is not given in the article cited.

In concluding this part of the subject, I wish to state that in my opinion great caution should be exercised in accepting the results obtained, so far as carbohydrates are concerned, when the germ has been grown on material containing carbohydrate.

Fat, Wax, etc. In the earlier investigations of the composition of bacteria, the alcoholic and ethereal extracts were often assumed to be fat, without further study. Kramer[41] notes that the

extract has the appearance of fat, and melts at not much over 40°. Hammerschlag[15] reports obtaining from the tubercle bacillus free fatty acids which melt at 63°, and concludes that the fat of this germ is mainly tripalmitin and tristearin, and that it contains little or no triolein. Nishimura[23] finds various fatty acids in his water bacillus. On evaporating the alcoholic and ethereal extracts, taking up the residue in alcohol, and cooling the solution, he obtains a soft, yellow, putty-like mass with the properties of lecithin. Meyer[38] rubbed up the dried germs at the proper stage of growth (when rich in fat) with quartz sand, and then extracted with ether. He obtained fat which he saponified. The resulting compound foamed on shaking with water. He found that the fat in bacillus tumescens gradually increases until spore formation takes place, then it disappears. He found no fat in the spores. Klebs[28] found in tubercle bacillus 20.5 per cent. of a red fat, melting at 42°, and 1.14 per cent. of white fat melting above 50°. The latter is insoluble in ether, but soluble in benzol. De Schweinitz and Dorset[31a] saponified fats obtained from the tubercle bacillus, and from the melting points of the acids conclude that the fat of this germ contains palmitic and arachidic acids, while that of the glanders bacillus contains oleic and palmitic. They also found a crystalline acid, for which they suggested tentatively the name tuberculinic acid, though this is quite different from Ruppel's nucleic acid. This fatty acid is obtained from the culture liquid and in small amount from the germ substance, but the method of extraction is not given. The crystals are prismatic, or needle-shaped, melting at 161–164°, readily soluble in alcohol, ether, and water. It does not give the biuret test. Analysis corresponds closely to the formula $C_7H_{10}O_4$. The authors call attention to the similarity in composition and properties of this body to teraconic acid, and suggest that this may be the substance which is responsible for coagulation necrosis, and that it is the temperature-reducing principle. In a later paper they describe a crude fat, extracted from tubercle bacilli. From this they obtained an acid which melted at 62°, and found the melting point unchanged by recrystallization. In summing up their work they conclude that the fat of the tubercle bacillus is principally a glycerid of palmitic acid. In addition there is a minute amount of the glycerid of a volatile fatty acid, to which tubercle bacilli cultures owe their characteristic

odor, a very small amount of an acid (probably lauric) melting at 42° to 43°, and an unusually high melting acid, an acid apparently with a larger carbon content than any before noted in plants. Ruppel[19] obtained three different extracts from the tubercle bacillus by using successively cold alcohol, hot alcohol, and ether. The first contained free fatty acids, and also fat melting between 55° and 60°, easily saponified and decomposed into free acid, and a higher alcohol. The second contained a waxy mass, hard to saponify, and which seemed to be the ester of a fatty acid, and a high alcohol. The third melted at 65° to 67°, and had an odor resembling beeswax. Aronson[42] obtained from tubercle bacilli, by means of a mixture of five parts of ether and one part of absolute alcohol, a yellowish-brown tenacious mass, constituting from 20 to 25 per cent. of the dried germ. From the growth of several hundred liters of culture 70 grams were obtained. This contained 17 per cent. of free fatty acids. The remainder was wax, that is, not acid and glycerin, but esters of acid and alcohol insoluble in water. Most of this wax is not in the cells, but lies around and between them. Levene[30] found about 30 per cent. of fat, or wax, in the tubercle bacillus.

Kresling[43] extracted the tubercle bacillus successively with ether, chloroform, benzol, and alcohol, and obtained 38.95 per cent. of fatty or waxy substances. Repeated extraction with chloroform gave a dark-brown mass of the consistency and color of beeswax and with a melting point at 46°. He found in this extract lecithin and cholesterin. His analysis showed the presence of 14.38 per cent. of free fatty acid, 77.25 per cent. of neutral fat and esters of fatty acids, and some volatile fatty acid—butyric. He regards the fat of the tubercle bacillus as quite different from that obtained from any other source.

The Reducing Action of Bacteria. Although the general subject of the reducing action of bacteria scarcely falls within the scope of this paper, it may be well to mention the work of two or three observers. Smith[44] found that many bacilli, including the colon, decolorize methylene blue, sodium indigo sulphate, litmus, etc. He concluded that this reducing action is common to all bacteria, both aerobic and anaerobic; that the velocity of reduction depends upon the number of the bacteria and the temperature; that it is a function of the bacterial plasma, and that the reducing substance does not dif-

fuse into the culture medium, but that the cell retains this property for a time after death.

Klett[45] tested the reducing action of bacteria on sodium selenate, tellurate, and some other salts. He also found that the reducing substance in the colon and other germs exists in the cell, and is not found among the cleavage products.

Jegunow[46] has shown that hydrogen sulphid is formed by the reducing action of bacteria on sulphates and on organic bodies containing sulphur. Sulphur bacteria oxidize hydrogen sulphid and store up the sulphur in the form of oily spheres which often constitute more than 90 per cent. of the cell substance. This sulphur is oxidized to sulphuric acid, thus serving as a source of energy for the vital processes of the organism. The sulphuric acid is neutralized by carbonates, and separated as a sulphate; then, by bacterial activity, the sulphate is reduced, thus forming a complete cycle. If the bacteria can obtain no sulphur they use that stored up in their cells, and then die in from one to two days.

The Cleavage Products of the Colon Bacillus. A discussion of the cleavage products of bacteria in general is beyond the scope of this paper, and I will confine myself to a brief statement of the work that has been done with the colon bacillus. The cleavage products of this germ are of special interest, inasmuch as it has been supposed by some that they play a rôle in the causation of the summer diarrheas of infancy. Baginsky[47] found the chief decomposition products of lactose by the colon bacillus to be acetic acid with smaller amounts of formic and lactic acids, and apparently traces of propionic and butyric acids; also traces of something, presumably acetone, giving iodoform with sodium hydrate and iodin. The same cleavage products were obtained under aerobic and anaerobic conditions, but in solutions of lactose containing no nitrogenous matter no acid was formed. Chantemesse and Widal[48] observed that the colon bacillus causes fermentation of lactose, saccharose, glucose, maltose, rhamnose, glycerin, erythrite, and mannite, but not of starch or glycogen. It uses up milk-sugar entirely if the acid formed is neutralized from time to time. Blumenthal[49] investigated the effect of varying amounts of alkali in colon cultures upon the cleavage products. He found that by increasing the alkalinity of the culture medium the yield of acid was increased, and he reports the presence of oxyacids, succinic,

and some volatile fatty acids. He also states that in milk cultures the higher the alkalinity the more acid is formed. He believes that the formation of substances harmful to the bacteria themselves is dependent upon the alkalinity of the culture, and that probably the formation of toxin is influenced by the amount of alkali. Harden[50] found that in the fermentation of glucose by the colon bacillus one-half the sugar becomes lactic acid and one-sixth of the carbon becomes alcohol, and one-sixth acetic acid. Small amounts of succinic and formic acids, hydrogen, and carbon dioxid are formed. The carbon dioxid formed varies from 12 to 18 per cent. of the sugar present. From 5 to 25 per cent. of the lactic acid produced is inactive, and from 95 to 75 per cent. of it is levorotatory.

Smith[51] investigated the production of gas in various media and found that in dextrose bouillon and in lactose bouillon hydrogen and carbon dioxid are produced approximately in the proportion of two to one by volume, and that the reaction becomes strongly acid. In saccharose bouillon the gas production takes place more slowly and is approximately three volumes of hydrogen to two of carbon dioxid, while the final reaction may be either acid or alkali, depending upon the rate of gas production. Pammel[52] arrived at corroborative results. Grimbert[53] found that the colon bacillus grown in bouillon containing potassium nitrate gives off amounts of nitrogen which are double that contained in the nitrate, and that nitrites cause the production of still larger quantities of nitrogen. The excess of nitrogen production in both cases is ascribed to the secondary action of nitrous acid upon amido compounds in the culture medium. Pennington and Küsel[54] analyzed the gases produced by the colon bacillus and found in glucose bouillon cultures small amounts of methane and nitrogen, together with hydrogen and carbon dioxid. Curiously enough, it was found that when the apparatus was filled with air deprived of oxygen, the other conditions remaining the same, no methane was obtained. There is a marked difference in the quantitative relations of the gases given off according to the age of the culture. Baginsky[47] tested 10 per cent. bouillon gelatin cultures and also milk cultures for extracellular toxin with negative results, and Vaughan[55] has shown the toxin to be intracellular.

Report of Experimental Work. The cultures used in these experiments were obtained from normal feces, and the virulence of

the germ was increased by passing it through a large number of animals. The germ substance was obtained in large amount by growth in the incubating tanks. In most cases these growths were about fourteen days old when removed, and the cultures were ordinarily grown at room temperature. The germ substance was scraped from the agar, extracted with alcohol repeatedly, dried between folds of filter-paper, then in vacuo over sulphuric acid, and pulverized. Long exposure to alcohol has a hardening effect on the cell substance, and at the first opportunity work will be undertaken with germ substance which has not been in contact with alcohol.

The germ substance prepared as above takes up moisture readily and holds it tenaciously, but by heating small amounts for many days in a steam-drying oven at from 85° to 95° it may be dried to constant weight. If the temperature runs down to 60° the substance may absorb moisture even in the oven. In the absence of apparatus for continuous heating at 105° to 110° the material was raised to 105° at intervals during two or three days, and left in a desiccator. Under this treatment it steadily increased in weight. The dried germ substance on burning forms volatile and liquid products, burns with a flame, gives off odors indicative of nitrogenous matter, and finally leaves a greenish ash. The following figures give the results of ash determinations: 0.346 g. of the germ substance gave 0.0296 g. ash, which is equivalent to 8.55 per cent. 0.496 g. of germ substance gave 0.0431 g. of ash, which is equivalent to 8.68 per cent. This is easily within the wide range found by others. The per cent. of ash found in the tubercle bacillus varies from 1.77 to 5.92 (De Schweinitz and Dorset,[31] Hammerschlag,[15] Levene[30]), while for other germs the values vary from 3 per cent. in putrefactive bacteria to 13 per cent. in prodigiosus; or by using special media, to nearly 30 per cent. (Nencki,[7] Kramer[41]).

A qualitative examination of the ash showed the presence of sodium, potassium, phosphates, and small but unquestionable amounts of calcium, aluminium, and copper. A slight residue insoluble in acid is doubtless silica. Sulphates and chlorids could not be detected. In bacillus prodigiosus, Kappes[36] found potassium and sodium and phosphoric acid, small amounts of calcium and magnesium, 0.66 per cent. of chlorin, and 0.07 per cent. of silica. In the cholera germ, Kramer[41] found potassium, sodium, phosphoric acid, a little cal-

cium, traces of magnesium, also sulphates and chlorids in amounts varying greatly according to the composition of the culture medium. De Schweinitz and Dorset[51a] made an analysis of the ash of tubercle bacilli grown upon neutral beef broth, and found neither sulphates, chlorids, nor carbonates, but large amounts of phosphoric acid, sodium, potassium, calcium, and magnesium. In comparison with the above, the results obtained for the colon bacillus are noteworthy only in the absence of magnesium and in the presence of copper and aluminium. Undoubtedly the copper comes from the tank.

The only constituent of the ash quantitatively determined was the phosphorus. In doing this the ash was dissolved in nitric acid, in which it was nearly all soluble. The phosphate was precipitated with ammonium molybdate, dissolved in ammonia, reprecipitated by magnesia mixture, and weighed as pyrophosphate. The following results were obtained: 0.496 g. of dried germ substance gives 0.0475 g. of magnesium pyrophosphate, which corresponds to 0.01323 g. of phosphorus, or 2.68 per cent. of the germ substance. 0.346 g. of the germ substance gives 0.0380 g. of pyrophosphate, or 0.01059 g. of phosphorus, showing the presence of 3.06 per cent. of phosphorus in the dried germ substance. The mean of these two determinations is 2.87 per cent. This agrees quite closely with Levene's results, who found 2.67 per cent. of phosphorus in the dried tubercle bacillus taken from mannite cultures. Kappes[56] reports 5.12 per cent. of phosphoric acid in prodigiosus. I interpret his statement as meaning this per cent. of P_2O_5, which would give approximately 2.2 per cent. of phosphorus. Other investigators have found smaller amounts of this element.

I will now turn to the more interesting study of the organic constituents. Referring again to work previously reported, we will recall that wax, fat, and lecithin have been obtained from alcoholic and ethereal extracts; protamin and nucleic acid from aqueous extracts; nucleoproteids, nucleic acid, and carbohydrate from extracts with dilute alkalies and solutions of neutral salts; xanthin bases and carbohydrates from acid extracts. Work upon the toxicity of the colon germ by Vaughan has emphasized the desirability of testing the action of dilute acid on the germ substance. Accordingly the pulverized germ substance after extraction with alcohol was treated with about forty times its weight of 1 per cent. sulphuric

acid. In some cases this mixture was shaken at ordinary temperature, and in some cases it was heated on the water bath. The most satisfactory results were obtained by rubbing the germ substance in a mortar with a small quantity of the acid and gradually adding more of the acid with constant stirring, then heating on the water bath for an hour. On standing a heavy deposit settled, leaving an opalescent supernatant fluid. Various expedients for filtering were tried but an ordinary hardened, folded filter proved most satisfactory. When such a filter is employed the first few cubic centimeters come through turbid, but as soon as the pores of the filter are filled the filtrate becomes a clear golden-brown. However, the filter gradually becomes clogged and filtration proceeds more slowly. A filter pump was tried, but was discarded because of the rapid filling of the pores of the paper with a gummy substance, and the practical stoppage of filtration. Whatever the expedient resorted to, filtration of the acid extracts of the dried germ substance proved to be slow, and with the paper which I have recommended it requires about five days to filter two liters.

The filtered acid extract was poured slowly into five volumes of 95 per cent. alcohol, with constant stirring, and gave a white, amorphous, flocculent precipitate which was at first very voluminous. This was allowed to settle for several hours, but it was found that the longer it stands in contact with alcohol the more imperfectly can it be dissolved in water. On the other hand, unless this precipitate completely subsides, filtration is slow. The precipitate thus obtained dissolves on stirring in a volume of water equal to the original volume of extract, and gives an opalescent solution which filters without difficulty and leaves no residue. This aqueous filtrate was reprecipitated by pouring into three volumes of absolute alcohol. I will designate this as precipitate A, and the alcoholic filtrates from both precipitates as B.

Precipitate A was allowed to settle as before and filtered as rapidly as possible, because it darkens on exposure to the air as long as it is moist. Here, again, the filter pump proved to be of no assistance, and filtering in an atmosphere of carbon dioxid was tried, but was found to be unsatisfactory.

The precipitate was dried between filters and then in vacuo over sulphuric acid. On drying it greatly diminishes in bulk and becomes

hard and horny in texture and gray in color, but when thoroughly pulverized it becomes lighter. It is worthy of note that of the acid extracts prepared under varying conditions no one gave a satisfactory biuret or Millon test. The extract prepared by shaking for one hour at room temperature gave negative results with potassium hydrate and copper sulphate, but on standing there was a slight reddish tinge. However, all of the extracts reduce nitric acid readily, and on the addition of ammonia give the typical xanthoproteic reaction. Ruppel[19] reports that all the extracts of the tubercle bacillus which he obtained gave very indistinct proteid reactions. He extracted with dilute alkalies, neutral salts and glycerin. However, Vaughan[55] found that on heating the unbroken colon germ on the water bath for an hour with 5 per cent. hydrochloric acid the extract gave a biuret test. I have found that treatment of the pulverized germ with alkali in the cold gives an extract which responds to the same test. Another general statement may be made here in order to avoid repetition: all extracts and their decomposition products give the α-naphthol test for furfurol, showing the presence of a carbohydrate.

The opalescent solution of precipitate A is acid to litmus and becomes clear and transparent on the addition of a trace of alkali. Phosphomolybdic acid and silver nitrate give precipitates, while albumin and ammoniacal silver nitrate do not. No free phosphate ions were found. On burning this there is about 32 per cent. of ash, which is nearly all soluble in nitric acid, and contains a large amount of phosphorus.

This substance A proves to be toxic, somewhat more toxic weight for weight than the whole germ. From repeated animal experiments the following are taken as typical examples: 100 mg. of the substance was dissolved in 10 c.c. of sterile water to which one drop of sodium hydrate solution was added. Guinea-pigs were injected intra-abdominally at 11.20 A.M., March 12th, as follows: No. 1 received 5 c.c., corresponding to 50 mg. of the substance; No. 2 received 2.5 c.c., corresponding to 25 mg. of the substance; No. 3 received 1 c.c., corresponding to 10 mg. of the substance; No. 4 received 0.5 c.c., corresponding to 5 mg. of the substance.

No. 1 was practically dead at 5 P.M. on the same day, although it did not actually draw its last breath until after 6 o'clock. No. 2

died at 6 P.M., while Nos. 3 and 4 were found dead at 7 o'clock the next morning. The postmortem findings were the same as those reported by Vaughan[55] as characteristic of the colon toxin.

Extracts obtained by heating with acid in the autoclave for one hour at from 140° to 144°, or by heating the moist fresh germ with acid on the water bath for two hours, gave similar precipitates with alcohol, but precipitates thus obtained were markedly less toxic than the one described above. The relative toxicity of the whole germ substance and that part of it split off with 1 per cent. sulphuric acid will be discussed in the paper by Marshall and Gelston. One hundred mg. of each of these less toxic precipitates was injected into the abdomen of a guinea-pig. In both cases the animal was very sick for a short time, but recovery followed. The chemical tests thus far applied have shown no difference between the toxic and the non-toxic substance split off from the cells by dilute acids under different conditions.

The residue after extraction with 1 per cent. sulphuric acid at ordinary temperature was again treated with the same strength of acid under the same conditions. The extract thus obtained gave a very slight precipitate when poured into absolute alcohol, but not enough to enable me to do any work with it. Again, the residue after extraction with 1 per cent. sulphuric acid on the water bath was thoroughly mixed with acid and heated in the autoclave to from 138° to 144° for one hour. This extract was poured into alcohol and found to give a small precipitate of only slightly toxic value. The residue from the last extraction was autoclaved for from three to four hours at from 140° to 144°, with 1 per cent. sulphuric acid, but in this way only a small amount of humin substance was obtained. The residue from the third extract was then autoclaved at from 140° to 144° for one hour, with 5 per cent. acid, and again nothing of value was obtained. These attempts to further extract toxin lead to the conclusion that a single extraction with 1 per cent. sulphuric acid is sufficient to split off all the toxic group which can be removed by this reagent.

A part of the acid extract is soluble in alcohol and consequently remains in the alcoholic filtrate. This filtrate, which I designate as filtrate B, was neutralized with sodium hydroxid. Much of the sodium sulphate was precipitated, carrying down with it considerable

organic matter. This precipitate was removed by filtration and the filtrate from it was distilled under diminished pressure at between 30° and 35°, until at last, when the temperature was run up to 50°. The residue, after distilling off the alcohol, consisted of a liquid which I will designate as C. C turned yellow on heating with potassium hydrate, but gave neither the biuret nor Millon's test. It also failed to reduce either Fehling's or Nylander's solution, but responded to the xanthoproteic and the α-naphthol tests. C yielded precipitates with ammonium molybdate, phosphomolybdic acid, ammoniacal silver nitrate, and picric acid. A guinea-pig was treated with 5 c.c. of C without effect. C was tested for xanthin bases in the following manner: on the addition of barium hydrate and barium chlorid it gave a precipitate D and a filtrate E.

E was treated with carbon dioxid in excess to remove the barium, and then boiled in order to dissipate the gas. The resulting solution still gives tests for furfurol and for bases. It was concentrated to about one-fourth its volume and precipitated with ammonia and ammoniacal silver nitrate. This precipitate was dissolved in boiling nitric acid, specific gravity 1.1, and allowed to stand forty-eight hours, but no crystals were found. The silver nitrate compound was concentrated, decomposed with hydrogen sulphid, filtered, and the filtrate evaporated and treated with ammonia. A precipitate was obtained which suggested xanthin. The silver sulphid precipitate was worked up for guanin, which might be carried down with the sulphid, and a small amount of an organic precipitate was obtained. Precipitate D was warmed with dilute sulphuric acid (1: 4) and the resulting solution found to contain carbohydrate, phosphate, and bases. After removing the phosphate, the bases were precipitated by ammoniacal silver. The silver compound was decomposed by hydrochloric acid. The acid solution gave a gelatinous precipitate with ammonia, soluble in excess of the reagent. In none of these experiments was the amount of precipitate sufficient for identification. However, I feel certain that one or more organic bases, presumably xanthin bodies, were present.

In another set of experiments the nitrogen in residue C was determined and found to be a little more than 1 mg. per c.c. Supposing that all of this nitrogen represents proteid, it would correspond to nearly 7 mg. of decomposed proteid in 1 c.c. of the solution. In

this experiment the distillation consumed several days, and the residue as obtained was left in the ice chest, where a considerable deposit formed. This was removed by filtration, dried, and still awaits investigation. The filtrate from this deposit was treated with hot concentrated barium hydrate until nearly neutral, distilled with magnesia to remove any ammonia formed, more barium hydrate added, and the excess of sulphate removed by filtration. The filtrate was acidified and xanthin bases precipitated by silver sulphate. The solution, after removing the xanthin bases, was treated for hexon bases according to the method of Kossel and Kutscher.[57] Excess of barium was added to the solution containing silver in order to precipitate arginin and histidin. The filtrate, after removing barium and silver, was concentrated and treated with sulphuric and phosphomolybdic acids. A fair amount of precipitate was obtained, and this was decomposed by barium hydrate and the excess of barium removed with carbon dioxid. On concentration a putty-like or gummy mass was obtained which, on treatment with picric acid, gave an oily deposit partially solidifying on standing and corresponding to the descriptions of lysin and its compounds.

The silver precipitate was treated for histidin, and I found an organic substance which turns yellow on evaporation with nitric acid. This substance taken up with silver nitrate gives an amorphous precipitate with ammoniacal silver. This compound was decomposed with hydrochloric acid, and after filtering out the chlorid of silver and concentrating the filtrate, crystals insoluble in water, but soluble in hydrochloric acid, were obtained. Here, again, I find evidences of bases. If they are hexon bases, lysin or an allied compound is the predominating one. The separation of xanthin and hexon bases by means of silver salts in acid solution is scarcely sharp enough to allow one to hazard an opinion until the individual bases have been obtained in sufficient quantities for more positive identification.

The residue left after extracting the moist fresh germ with 1 per cent. sulphuric acid was thoroughly mixed with 33⅓ per cent. sulphuric acid, and boiled for eight hours with reflux condenser. The black extract was filtered. Here, and in all cases where an inorganic precipitate like barium sulphate or silver sulphid was obtained, the precipitate was repeatedly boiled with water, filtered, and the filtrates added to the original. Barium hydrate was added to the extract

until about half the acid was neutralized. After filtering out the barium sulphate the resulting filtrate does not give the biuret test, yields no precipitate with alcohol, and gives no reduction with Fehling's solution. Millon's reagent gives a solution which turns red on heating, yellow on boiling, and gives a tan-colored precipitate. With nitric acid there is vigorous action, and the subsequent addition of ammonia brings out a faint xanthoproteic test. Silver nitrate and ammoniacal silver nitrate give precipitates. α-naphthol gives a good ring, but this is brown rather than red.

The liquid was concentrated on the water bath to about one-sixth its volume, but no crystals (of tyrosin) formed. Much of the acid was removed by means of barium, but the solution was left distinctly acid. Phosphotungstic acid was added in order to obtain the bases free from interfering substances. When this solution was precipitated while hot and allowed to stand for twelve hours a heavy crystalline precipitate formed. This precipitate was suspended in hot water, hot saturated barium hydrate added to slight alkaline reaction, filtered, the filtrate treated with carbon dioxid in order to remove the barium, and then boiled in order to drive off the gas. The resulting solution was worked up for xanthin and hexon bases according to Kutscher's[58] method. The precipitate of xanthin bases seemed considerable, but on drying proved to be too little for positive identification. A goodly precipitate was obtained which corresponded to histidin silver. This was decomposed with hydrochloric acid and crystalline plates obtained. A gelatinous mass corresponding to arginin and a residue which should be lysin await further investigation.

The residue after repeated extraction with acid was treated with from 2 to 4 per cent. of sodium hydrate either upon the water bath or over a free flame. In every case the substance went into solution readily, leaving only a slight coating on the filter. In one case this slight residue was removed from the filter, and an approximate determination made. The total residue was about 0.4 g., which was equivalent to 0.8 per cent. of the germ substance used. The organic matter was only 0.15 g., equivalent to 0.3 per cent. of the original. This residue gave no proteid test, contained no nitrogen, and proved to be a carbohydrate.

The alkaline extract was neutralized with hydrochloric acid and then added to three volumes of 95 per cent. alcohol. A light-colored,

flocculent precipitate G was obtained. This turned dark on exposure to the air, incident to filtration. It was dissolved in 0.5 per cent. potassium hydrate and reprecipitated twice. Each time the fresh precipitate was white or nearly so, but the utmost care in filtering even in an atmosphere of carbon dioxid did not suffice to prevent its turning dark. The solution in 0.5 per cent. potassium hydrate gave the xanthoproteic and furfurol tests, and was precipitated by copper chlorid. It failed to respond to the biuret and Millon's test and did not give precipitates on the addition of either picrid acid or platinum chlorid. This solution was acidified with picric acid and acetic acid, copper chlorid added and the mixture poured into three volumes of alcohol. The resultant precipitate dissolved in water did not reduce Fehling's solution until it had been boiled with hydrochloric acid, after which it also reduced Nylander's solution and gave the furfurol test. This again indicates the presence of carbohydrate.

A sample of G burned readily, puffing up and glowing in the manner characteristic of nucleic acid, then fused and finally left a dark ash. Two determinations of phosphorus were made with the following results:

0.4723 g. of the substance yielded 0.0524 g. magnesium pyrophosphate, corresponding to 0.0145 g. of phosphorus. Phosphorus equals 3.09 per cent.

0.6469 g. of the substance yielded 0.0685 g. of magnesium pyrophosphate, corresponding to 0.01895 g. of phosphorus. Phosphorus equals 2.93 per cent.

These figures indicate that the substance is a nuclein body rather than free nucleic acid.

SUMMARY. The dried germ substance after extraction with alcohol yields 8.6 per cent. ash. One-third of the ash is phosphorus, while sodium and potassium are the most abundant metals. The acid extract is in part soluble in alcohol, and in part insoluble. The insoluble portion contains carbohydrate, nucleoproteid or its decomposition products, bases, and much phosphorus. It is quite toxic, although it is uncertain whether the toxicity belongs to the body of the precipitate or is due to a smaller amount of virulent toxin mechanically carried down. The soluble portion also contains carbohydrate, bases, and phosphate. The alkaline extract contains carbohydrate and a nuclein body.

The work has not progressed far enough to justify the drawing of definite conclusions. But if we consider the germ substance as made up chiefly of glyconucleoproteid, it affords a satisfactory explanation of the facts observed by others as well as myself. According to the conditions, one would obtain carbohydrate, nuclein, nucleic acid, xanthin bases, hexon bases, protamin, and phosphate. The extracts formed under varying conditions show great similarity. The differences are doubtless due to carrying the cleavage action further in some cases than in others. I have found no protamin, but the measures used were doubtless too violent. I have also found no evidence of cellulose.

In comparing results recorded in the literature, it should be remembered that in some of the earlier work the nitrogenous matter was assumed to be a simple proteid, and any excess of carbon was assumed to be cellulose.

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PART VI.—THE TOXICITY OF THE CELLULAR SUBSTANCE OF THE COLON BACILLUS.

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These experiments were begun by one of us (Marshall) in June, 1901, and were continued by the other (Gelston) after the middle of August of the same year. The material employed in determining the toxicity was grown in the incubating tanks, removed after fourteen days, repeatedly extracted with alcohol and ether, dried in the air, and rubbed to a powder in a mortar. The same batch of material was used in all experiments mentioned in this paper. The powder

was suspended in water, and the suspension boiled for a few minutes before injection in order to ensure complete sterilization. The first experiments were made with the germ substance reduced to a coarse powder by attrition in a porcelain mortar.

TABLE I.—*The Toxicity of the Coarsely Powdered Germ Substance of the Colon Bacillus when Injected Intraperitoneally into Guinea-pigs.*

Protocol number.	Weight.	Amount of material injected.	Result, hrs.	Proportion of toxin to body weight.
35	162 g.	10.80 mg.	+ 12	1 : 15,000
36	195	13	+ 12	
47	555	37	+ 12	
48	472	31.46	+ 18	
4			4 + in 12 to 18 hours.	
33	212	10	+ 12	1 : 20,000
34	202	10.10	+ 12	
45	452	22.30	+ 12	
46	422	21.10	+ 12	
4			4 + in 12 hours.	
31	165	6.60	+ 12	1 : 25,000
32	203	8.12	+ 12	
43	675	27	+ 12	
44	410	16.40	+ 12	
4			4 + in 12 hours.	
29	184	6.13	+ 12	1 : 30,000
41	545	18.16	+ 12	
42	470	15.66	— (an old, used pig).	
30	180	6	+ 12	
4			3 + in 12 hours. 1 —	
27	183	5.54	+ 12	1 : 35,000
39	465	13.28	+ 12	
28	189	5.69	+ 12	
40	665	18.71	+ 12	
4			4 + in 12 hours.	
25	225	5.65	+ 12	1 : 40,000
26	192	4.8	+ 12	
37	662	16.55	— (an old, used pig).	
38	825	20.62	+ 48	
4			2 + in 12 to 48 hours. 1 —	

Protocol number.	Weight.	Amount of material injected.	Result hrs.	Proportion of toxin to body weight.
21	315	6.30	—	1 : 50,000
22	268	5.36	—	
23	262	5.24	—	
24	287	5.74	—	
4			4 —	
17	268	2.68	—	1 : 100,000
18	317	3.17	—	
19	270	2.70	—	
20	245	2.45	—	
4			4 —	
13	255	1.275	—	1 : 200,000
14	283	1.465	—	
15	235	1.675	—	
16	249	1.245	—	
4			4 —	
9	256	0.765	—	1 : 333,333
10	273	0.819	—	
11	230	0.690	—	
12	220	0.660	—	
4			4 —	
5	225	0.450	—	1 : 500,000
6	235	0.470	—	
7	245	0.490	—	
8	295	0.590	—	
4			4 —	
1	212	0.212	—	1 : 1,000,000
2	256	0.256	—	
3	261	0.261	—	
4	194	0.194	—	
4			4 —	

It will be seen from the above given figures that the coarsely-powdered germ substance kills practically all the pigs in the proportion of 1 : 40,000 or in larger amounts, and fails to kill when the proportion is 1 : 50,000, or less.

Next, the germ substance was rubbed up to a much finer powder in an agate mortar, and then injected as before.

TABLE II.—*The Toxicity of the Finely Powdered Germ Substance of the Colon Bacillus when Injected Intraperitoneally into Guinea-pigs.*

Protocol number.	Weight.	Amount of material injected.	Results, hrs.	Proportion of toxin to body weight
61	172 g.	4.09 mg.	+ 12	1 : 42,000
62	170	4.05	+ 12	
2			2 + in 12 hours.	
63	165	3.66	+ 12	1 : 45,000
64	165	3.66	+ 12	
2			2 + in 12 hours.	
65	180	3.83	+ 12	1 : 47,000
66	170	3.61	+ 12	
2			2 + in 12 hours.	
67	220	4.4	+ 12	1 : 50,000
68	152	3.04	+ 12	
2			2 + in 12 hours.	
128	215	2.86	—	1 : 75,000
129	195	2.6	+ 4 days.	
130	175	2.33	+ 12 hours.	
131	180	2.04	+ 12	
132	135	1.8	+ 12	
133	230	3.06	+ 12	
134	170	2.266	+ 12	
135	145	1.98	+ 12	
8			7 + in 12 hrs. to 4 days. 1 —	
104	195	1.95	—	1 : 100,000
105	275	2.75	—	
106	305	3.05	—	
107	232	2.32	—	
108	430	4.30	+ 7 hours.	
109	255	2.55	—	
110	270	2.70	+ 19 hours.	
111	215	2.15	+ 20	
120	175	1.75	—	
121	218	2.18	+ 8 days.	
122	130	1.30	—	
123	220	2.20	—	
124	270	2.70	+ 9 hours.	
125	190	1.90	—	
126	235	2.35	+ 7 days.	

Protocol number.	Weight.	Amount of material injected.	Results, hrs.	Proportion of toxin to body weight.
127	135	1.35	—	
49	183	1.83	—	
50	163	1.63	+	12 hours.
51	153	1.53	—	
52	275	2.75	—	
53	268	2.68	—	
54	238	2.38	—	
55	253	2.53	—	
56	212	2.12	—	
57	340	3.40	—	
58	297	2.97	+	12 hours.
59	170	1.70	—	
60	145	1.45	+	12 hours.
28			9 + in	7 hrs. to 8 days.
			19 —	
112	265	0.1325	+	12 hrs. 1 : 200,000
113	155	0.775	+	50
114	210	0.105	+	10 days.
115	175	0.875	+	4
116	140	0.7	—	
117	165	0.825	+	12 hours.
118	185	0.925	—	
119	195	0.975	—	
8			5 + in	12 hrs. to 10 days.
			3 —	
69	200	0.1	—	1 : 2,000,000
70	175	0.085	—	
71	162	0.081	—	
72	520	0.26	+	48 hours.
73	805	0.4025	—	
74	400	0.200	—	
75	590	0.295	—	
76	495	0.24725	—	
77	370	0.185	—	
78	455	0.2775	+	48 hours.
79	685	0.3425	+	72 hours.
80	665	0.3375	—	
81	615	0.3075	—	
82	600	0.300	—	
83	725	0.3625	—	
84	500	0.250	—	
85	610	0.305	—	
86	695	0.3475	+	24 hours.

Protocol number.	Weight.	Amount of material injected.	Results, hrs.	Proportion of toxin to body weight.
87	585	0.2975	—	
88	385	0.1975	—	
89	695	0.3475	—	
90	860	0.430	—	
91	265	0.1325	—	
92	715	0.3575	—	
93	140	0.700	—	
94	885	0.4425	—	
95	340	0.170	—	
96	250	0.125	—	
97	215	0.1075	—	
98	255	0.1275	—	
99	230	0.115	—	
100	250	0.125	—	
101	355	0.1755	—	
102	255	0.1275	—	
103	272	0.136	—	
34			30 — : 4 + in 48 to 72 hrs.	

The figures in Table II. when compared with those in Table I. show unquestionably that the more finely divided powder is more toxic. We believe that this is due to the more ready solubility of the finely divided powder in the fluids of the body. We desire to call attention to the fact that in this set of experiments there is a considerable percentage of deaths among the animals which received very small doses. We cannot explain this except upon the ground of individual susceptibility. Every animal was carefully examined after death, and in no case could there be found any cause of death other than the action of the poison.

The finely divided germ substance was next suspended in water, and heated in the autoclave for fifteen minutes at 2 kilos pressure (134°).

TABLE III.—*The Toxicity of the Heated Germ Substance of the Colon Bacillus when Injected Intraperitoneally into Guinea-pigs.*

Protocol number.	Weight.	Amount injected.	Result, hrs.	Proportion of toxin to body weight.
136	175 g.	7.0 mg.	+ 8	1 : 25,000
137	180	7.2	+ 9	
138	210	8.4	+ 6¼	
139	165	6.6	+ 6¼	
140	175	7.0	+ 20	
5			5 + in 5 to 20 hours.	

Protocol number.	Weight.	Amount injected.	Result, hrs.	Proportion of toxin to body weight.
141	160	3.2	+ 22 hours.	1 : 50,000
142	155	3.1	+ 8	
143	130	2.6	+ 8	
144	160	3.2	+ 8	
145	155	3.1	+ 8	
146	120	2.4	+ 8	
6			6 + in 8 to 22 hours.	
147	140	1.866	+ 22 hours.	1 : 75.000
148	140	1.866	+ 8	
149	170	2.1266	+ 8	
150	160	2.1133	+ 8	
151	135	1.8	+ 13 days.	
152	150	2	+ 22 hours.	
6			6 + in 8 hours to 13 days.	

The above given results show that heating the germ substance suspended in water to 134° for fifteen minutes did not appreciably lessen its toxicity.

TABLE IV.—*The Toxicity of the Germ Substance of the Colon Bacillus when Injected Intraperitoneally into Rabbits.*

Protocol number.	Weight.	Amount injected.	Result, hrs.	Proportion of toxin to body weight.
39	1325 g.	17.66 mg.	+ 12 hrs.	1 : 75,000
40	980	13.06	+ 12 hours.	
41	1075	14.33	—	
42	535	7.13	—	
4			2 + in 12 hours.	2 —
1	2660	26.6	—	1 : 100,000
2	1687	16.87	—	
3	2690	26.90	+ 12 hours.	
4	2232	22.32	+ 12 hours.	
5	2060	20.60	—	
6	2485	24.85	+ 12 hours.	
7	2320	23.20	+ 72 hours.	
7			4 + in 12 to 72 hours:	3 —

Protocol number.	Weight.	Amount injected.		Result, hrs.	Proportion of toxin to body weight.
8	2435	12.17	+	5 hours.	1 : 200,000
9	1907	9.535	—		
10	2390	11.95	+	18 hours.	
11	1530	7.65	+	5 hours.	
12	2080	10.40	—		
13	2070	13.65	+	24 hours.	
14	2130	10.65	—		
33	1185	5.925	—		
34	935	4.675	—		
35	535	2.675	—		
36	460	2.30	—		
37	675	3.375	—		
—					
12			4 + in 5 to 24 hours : 8 —		
15	800	0.40	—		1 : 2,000,000
16	842	0.421	—		
17	1117	0.5585	—		
18	900	0.450	—		
19	1115	0.5575	—		
20	1180	0.590	—		
21	875	0.4375	+	12 hours.	
22	785	0.3925	+	12 hours.	
23	885	0.4425	—		
24	955	0.4775	—		
25	920	0.460	—		
26	1570	0.735	—		
27	920	0.460	—		
28	1075	0.5375	—		
29	880	0.440	—		
30	960	0.480	—		
31	885	0.4425	—		
32	1340	0.670	—		
—					
18			2 + in 12 hours : 16 —		

It should be stated that the finely powdered germ substance was employed in all the experiments made upon rabbits.

One gram of the dried germ substance was incinerated, and the total resulting ash was injected intraperitoneally into a guinea-pig without effect.

The toxic action of the germ substance when injected subcutaneously is practically the same as when injected intraperitoneally, but death is not so prompt.

The relative toxicity of the whole germ substance, and the poison split off with dilute acids has not been sufficiently studied to enable us to make any positive statements at present. In one experiment, 50 g. of the germ substance used in the tables already given yielded about 5 g. of the substance split off with dilute sulphuric acid, and precipitated with alcohol, and 0.1 mg. of this substance killed guinea-pigs weighing from 200 to 300 g. However, we have found marked differences in the toxicity of the split product, even when obtained from the same germ substance. This, undoubtedly, is due to the fact that prolonged heating decreases the toxicity of the split product. It should also be remembered in making comparisons between the toxicity of the whole germ substance, and that of the group split off with dilute acid, that the latter exists in the form of a sulphate, and that in round numbers one-third of it is inorganic matter. Neither have we studied with sufficient exactness the relative toxicity of the whole germ substance, and that of the residue left after extraction with dilute acid. However, we can say that the residue of the germ substance left after extraction with dilute acid possesses less than one-tenth of the toxicity of the whole germ substance.

We have carried out a long series of experiments upon both guinea-pigs and rabbits for the purpose of establishing immunity to the entire germ substance. For want of space we will sum up the results which we have obtained in these experiments as follows:

1. Although guinea-pigs and rabbits acquire immunity to the germ substance but slowly, yet if sufficient time be given, and the animal be allowed to recover before a second dose is administered, a fair degree of immunity may be obtained after many months of treatment. Unless the animal be allowed to completely recover before a second injection is given, death generally results. In these experiments for the purpose of inducing immunity, we employed the finely-divided powdered germ substance, which had been used in determining the toxicity. Our previous experiments had shown that one part of the finely-divided powder to 75,000 parts of body weight in guinea-pigs was surely fatal. Guinea-pig No. 93 received on the fifteenth injection a dose of 28 mg. (1 : 17,321), and recovered from the same. Guinea-pig No. 109 received on the ninth injection 25.5 mg. (1 : 22,745), and recovered. Rabbit No. 27 received on the twelfth injection 184 mg. (1 : 10,625), and recovered. Rabbit No.

17 received on the fifteenth injection 372.3 mg. (1 : 4780), and recovered. Rabbit No. 29 received on the thirteenth injection 293.3 mg. (1 : 6409), and recovered.

A study of the blood serum obtained from animals partially immunized to the germ substance led to the following results:

(*a*) The blood serum of Rabbit No. 2, which had received on the twelfth injection 562.3 mg. (1 : 3503), obtained twenty days after the last injection, had no bacteriolytic action on the organisms contained in a beef-tea culture of the colon bacillus of the same strain as that which had been used in immunizing the animals.

(*b*) Tubes of immune serum, and others of normal serum, were inoculated with virulent cultures of the colon bacillus, and placed in the incubator at 37.5°. Both sets of tubes showed a good and equal growth within seven hours.

(*c*) Tubes of I. S. and N. S. were inoculated with virulent cultures of colon and typhoid bacilli, and from these gelatin plates were made at the end of one minute, thirty minutes, one hour and forty-eight hours. The number of colonies on the colon plates did not diminish, while those on the typhoid plates did with both sera, thus showing that the I. S. had no specific action.

(*d*) I. S. when mixed with filtered cultures of the colon bacillus gives a slight precipitate, which, however, is also given by normal serum.

(*e*) The I. S. gives very positive agglutinating reactions with suspensions of the dead colon germ used in immunizing the animals. Suspensions of from 1 to 50 mg. of the germ substance in 1 c.c. of physiologic salt solution are completely precipitated in from three to five minutes on the addition of an equal quantity of I. S. Control tubes to which N. S. had been added gave negative results, inasmuch as complete subsidence did not occur in these within fourteen days.

(*f*) The I. S. exerts when mixed with suspensions of the germ substance and injected into the abdominal cavity of rabbits a slight protective action, as is shown by the following:

Rabbit No. 1	850 g. had 17 mg. (1 : 50,000) + 2 c.c. I. S.	—
2	700 g. had 14 mg. (1 : 50,000) + 2 c.c. N. S.	+
3	840 g. had 16.8 mg. (1 : 50,000) + 2 c.c. beef tea	+

(*g*) The I. S. of the rabbit exerts no protective action for the guinea-pig against the germ substance.

3. The immunity obtained by treating animals with the germ substance is apparently of short duration, and if the interval between the administration of doses be prolonged, death is likely to follow even when there is no increase in the size of the dose. It will thus be seen that the attempt to immunize animals to the germ substance of colon bacillus is beset with difficulties. If the intervals be too short, and the animal has not fully recovered, death is likely to result, and the same will also probably happen when the interval is unduly long. Even after a marked degree of immunity has been obtained this is apparently lost within a few weeks, and a repetition of a dose of the same size causes death. The following table, showing next to the last, and the last injections given to certain animals, will illustrate our meaning:

Jan. 18, 1902,	Rabbit 17,	1780 g.	had 372.3 mg.	(1 : 4,780)	and recovered
Mar. 29, 1902,	Rabbit 17,	1880 g.	had 372.3 mg.	(1 : 5,048)	and died March 31.
Jan. 18, 1902,	Rabbit 29,	2000 g.	had 293.3 mg.	(1 : 6,819)	Recovered.
Mar. 29, 1902,	Rabbit 29,	1880 g.	had 293.3 mg.	(1 : 6,409)	Died March 31.
Jan. 6, 1902,	Pig 93,	485 g.	had 28.0 mg.	(1 : 17,321)	Recovered.
Mar. 29, 1902,	Pig 93,	645 g.	had 28.0 mg.	(1 : 19,464)	Died March 31.

Although we have made a few experiments in attempting to immunize animals, both to the toxin split off with dilute acids, and to the residue left after extraction with dilute acids, we are not as yet ready to give the results obtained.

PART VII.—THE INTRACELLULAR TOXIN OF THE DIPHTHERIA BACILLUS.

By LOUIS M. GELSTON, A.B.,
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The germ substance of the diphtheria bacillus used in these experiments was obtained by growths in Roux flasks on ordinary agar containing an excess of from 7 to 10 c.c. of normal sodium hydrate. We have made two or three attempts to grow the diphtheria bacillus on the large tanks, but the yield has not been satisfactory. This is probably due to imperfect aeration. The Roux flasks after steriliza-

tion were inclined, and after having been proved to be sterile by submitting them to a twenty-four-hour period of incubation were inoculated with from 2 to 3 c.c. of a bouillon culture of the diphtheria bacillus twenty-four hours old. The cultures used were two in number and quite different in toxicity, as will be seen by subsequent details.

After incubating for from seven to nineteen days at 37.5° the growth was scraped from the surface of the agar by means of glass rods bent twice at right angles, once four inches from one end, and again one inch from the first bend.

The fresh germ substance scraped from the surface of the agar in the flasks was immediately placed in sterile physiologic salt solution, and then heated for two and a half hours at 50° in order to secure sterilization. This suspension was then poured onto hard filter-paper, and placed in an ice chest until filtration was complete. The mass of germ substance thus collected was washed with physiologic salt solution or distilled water, poured onto a porous plate, dried over sulphuric acid in vacuo, and finely powdered in an agate mortar. The physiologic salt solution extract obtained as a filtrate was passed through a Chamberland filter and injected into animals. Intraperitoneal injections of from 5 to 10 c.c. of this extract produced in all cases a marked reaction, but was never fatal. This was to be expected on account of the relatively large amount of salt solution used for extraction, which amounted to from 250 to 1000 c.c. for every gram of germ substance. If after the removal of the germ substance from the agar in the Roux flasks sterile salt solution be poured into each flask and the agar left to digest in this for twenty-four hours, the resulting liquid after filtration through a Chamberland filter is fatal to guinea-pigs in from twelve to thirty-six hours after an intraperitoneal injection of from 5 to 10 c.c.

Various samples of diphtheria germ substances have been prepared as above, and all have proven more or less toxic, killing guinea-pigs in proportion of 1 : 6100 body weight to 1 : 33,000 in from twelve to thirty-six hours after intraperitoneal injection. Subcutaneous injections have proven equally but more slowly fatal. On postmortem examination all animals dying after intraperitoneal injection show marked congestion of the mesentery, omentum, peritoneum, and adrenal body ; also numerous ecchymoses and hemorrhagic effusions in the serous membrane of the stomach, intestine, and peritoneum. The

spleen, liver, and kidney appear to be somewhat enlarged, and are dark in color. In the kidneys a dark line sharply divides the cortex from the medulla. The heart is in diastole.

If mixtures of commercial diphtheria antitoxin and suspensions of the germ substance in physiologic salt solution be injected into the abdominal cavities of guinea-pigs death follows as rapidly as if the germ substance alone had been injected. One thousand immunity units fail to exert any protective influence against 10 minimum lethal doses of the germ substance, as is shown by the following tables:

TABLE I.—*Showing the Effects of Injections of Mixtures of the Intracellular Toxin of Diphtheria and Commercial Diphtheria Antitoxin.*

Proto. No.	Wgt.	Amt. injected.	Antitox.[1]	Antitox.[2]	I. U.	Result.
1	155	47.1=3300	0.0005 c.c.	0.00031 c.c.	0.118	+ 12 hours.
2	135	40.9	0.005	0.0029	1.175	+ 12 "
3	200	60.6	0.0242	0.0194	5.7	+ 12 "
4	150	46.0	0.05	0.03	11.75	+ 12 "
5	135	40.9	0.2	0.109	47.0	+ 12 "
6	175	53.0	0.5	0.35	117.5	+ 12 "
7	120	37.0	1.0	0.48	235.0	+ 12 "
8	120	37.0	2.0	0.96	470.0	+ 12 "

NOTES. In these experiments the minimum lethal dose of the intracellular toxin was 1 : 33,000 parts of body weight, and 1 c.c. of antitoxin was equivalent to 235 immunity units.

With another germ powder and a fresh sample of antitoxin, a second experiment confirmed the one just reported.

TABLE II.—*Showing the Effects of Injections of Mixtures of the Intracellular Toxin of Diphtheria and Commercial Diphtheria Antitoxin.*

No.	Wgt.	Toxin.	Antitox.	Tox. cor.	Antitox. cor.	I. U.	Result.
1	257 g.	553.9 mg. (1=464)	2.5 c.c.	553.9 mg.	2.568 c.c.	1000	+ 12 hrs.
2	280	0.05 c.c. = 10	0.0025	0.056 c.c.	0.0028	1	—
3	245	52.8 (1=4640)		Control.			+ 12 hrs.

In these experiments Pig No. 2 received 10 minimum lethal doses of a filtered bouillon culture of the same germ from which the powdered germ substance was obtained, and also one immunity unit of commercial antitoxin. In other words, these experiments show that

[1] Antitoxin for 250 grams of body weight.
[2] Antitoxin for actual body weight.

while commercial diphtheria antitoxin protects animals against the extracellular toxin of diphtheria, it fails to afford protection against the intracellular toxin.

When the dried cellular substance of the diphtheria bacillus is treated with a 1 per cent. by weight solution of sulphuric acid in water there is split off from the diphtheria cell a more or less poisonous substance, which is probably identical with the toxin found in filtered bouillon cultures. I obtained some powdered diphtheria germ substance, and having ascertained that the minimum lethal dose of this powder was 1 : 33,000 parts of body weight, I weighed out 500 mg. of this powder, placed it in a beaker, covered it with 100 c.c. of a 1 per cent. weight solution of sulphuric acid, and digested on the water bath for one hour, after which the mixture was passed through a hard filter, and the perfectly clear filtrate allowed to fall into two volumes of 95 per cent. alcohol. A white flocculent precipitate formed and was collected on filter-paper. This was thoroughly washed with alcohol, then dried in vacuo, finely pulverized in an agate mortar, then suspended in physiologic salt solution and injected intraperitoneally into guinea-pigs as follows:

No. 1	400 g.	had 100 mg.	+ in 8 hours.
2	170 g.	had 100 mg.	+ in 4 hours.

In another experiment I took 3.988 g. of dried diphtheria germ substance, placed it in a beaker, covered it with 400 c.c. of 1 per cent. sulphuric acid, and extracted for twenty-four hours in the cold. The supernatant liquid was then poured off through hardened paper, and the filtrate allowed to run into two volumes of 95 per cent. alcohol. The alcohol produced a white precipitate, which was collected, washed with alcohol, dried, powdered, suspended in physiologic salt solution, and injected intraperitoneally into guinea-pigs as follows:

No. 1	195 g.	had	20 mg.	(1 : 9750)	—
2	170 g.	had	50 mg.	(1 : 3400)	Sick, but recovered.
3	200 g.	had	100 mg.	(1 : 2000)	" "
4	195 g.	had	170 mg.	(1 : 1148)	+ 3 hours.

The low toxicity of this split-off product is in part due, I think, to the length of time to which it was exposed to the action of the dilute acid.

In the few experiments made commercial antitoxin apparently does protect animals against the toxin which is split off from the cell

by dilute acid. However, the number of experiments that we have made on this point is too small to justify any positive statement.

A second extraction of the germ substance with dilute acid fails to remove anything, thus indicating that the group removable by hydrolysis with dilute acids is completely removed on the first extraction. Some of the residue left after the second extraction of the germ substance with dilute acid was dried, pulverized, and injected into guinea-pigs as follows :

No. 1	Weight 195 g.	had	58.5 mg.	(1 : 3333)	+	36 hours.
2	Weight 195 g.	had	44.7 mg.	(1 : 4362)	+	5 days.

Commercial antitoxin has no protective influence against the germ substance left as a residue after extraction with dilute acid, as the following experiment will indicate: A guinea-pig weighing 250 g. received 574 mg. of the residue left after two extractions with acid. This was equivalent to ten minimum lethal doses. This animal also received 8 c.c. of commercial diphtheria antitoxin, which was equivalent to 1000 immunity units, and the animal died within seven hours.

Suspensions of the diphtheria germ substance when exposed to a temperature of 50° or higher, for fifteen minutes or longer, gradually decrease in toxicity. However, the toxicity is not altogether destroyed, even after an exposure for thirty minutes to a temperature of 120° in the autoclave. The minimum lethal dose of a certain powdered germ substance having been found to be 1 : 33,000, it was heated for twenty minutes to 122°, after which the minimum lethal dose was found to be 1 : 6400.

Probably the most interesting fact which I have ascertained in this study is that those cultures which yield the most powerful extracellular toxins do not give the most toxic germ substance. As was stated in the beginning, I have employed in these experiments two cultures, one of which (Park's No. 8) gives a most active bouillon culture, but furnishes a germ substance which is but slightly toxic. The other culture which I have employed gives a weak bouillon toxin, but furnishes a more powerful intracellular poison.

PART VIII.—THE ANTHRAX TOXIN.

By J. WALTER VAUGHAN, A.B.,
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In the history of the study of the infectious diseases, anthrax must always hold a prominent position. Indeed, this disease has generally been recognized as one of the most typical of the infectious group, and no theory concerning the nature of these diseases can be complete until it has been determined whether or not it is applicable to anthrax. It may be of interest to briefly state some of the views held concerning the nature and origin of this disease before its infectious character was established, and its specific cause discovered. In 1805, Kausch[1] wrote a monograph on anthrax, in which he held that this disease is due to paralysis of the nerves of respiration, but he offered no explanation of the cause of this paralysis. Delafond[2] held that anthrax has its origin in the influence of the chemical composition of the soil affecting the food of animals, and inducing pathologic changes from altered nutrition. The studies of Gerlach[3] in 1845 established quite conclusively the contagious nature of this disease. This was emphasized by Heuzinger[4] in 1850, and accepted by Virchow[5] in 1855; but as early as 1849 Pollender[6] had examined the blood of cows dead with anthrax, and had seen the bacilli. Pollender's paper was not published until 1855, but he states that the observations recorded were made in the fall of 1849. He examined the blood of five cows dead from anthrax and used blood taken from the spleen of a healthy animal for control purposes. The microscopic examinations were made between eighteen and twenty-four hours after death, and the blood was stinking, thus indicating that it had become contaminated with putrefactive bacteria. Pollender used a compound microscope made by Plössl, and he gave his attention to the blood corpuscles, chyle globules, and the bacilli. The following is a condensed statement of his description of the micro-organisms: The third and most interesting microscopic bodies seen in anthrax blood

are innumerable masses of rod-like, solid, opaque bodies, the length of which varies from $\frac{1}{400}$ to $\frac{1}{200}$ of a line, and the breadth averages $\frac{1}{8000}$ of a line. They resemble the "vibrio bacillus" or "vibrio ambiguous." They are non-motile, and neither water nor dilute acids nor strong alkalies have any effect upon them. Concerning the origin and nature of the bacilli, Pollender claimed no knowledge, and he asked the question whether they are present in the blood of the living animal, or should be considered a product of putrefaction; also, whether they might be considered the infection itself, or merely the bearer of infection, or whether they had anything to do with the infection. After studying the action of acids and alkalies upon them he came to the conclusion that they belong to the vegetable world. It will be seen from the above that while so far as we know Pollender was the first to detect bacilli in anthrax blood, he made no investigations concerning the relation of these organisms to the disease. In 1856, Brauell[7] inoculated sheep, horses, and dogs with blood taken from animals sick and dead with anthrax, and demonstrated that the disease could be transmitted in this way to the sheep and horses, but not to the dogs. Sheep were found to be highly susceptible, horses much less so, and dogs quite immune. Brauell not only studied the vibrio which had first been seen by Pollender, but demonstrated its presence in the blood of the animals sick with anthrax before death. It is interesting to note that Brauell fell into an error, inasmuch as he stated that the vibrios as first seen in the blood were non-motile, but later became highly motile. Of course, we now know that the motile bacilli seen by Brauell after the blood had stood for some days were not anthrax bacilli, but owed their presence to contamination. It should be noted that Brauell also made examinations of the blood of various domestic animals suffering from other diseases, and proved the absence of the anthrax bacillus except in anthrax. In 1863 Davaine[8] published three most valuable papers on anthrax. In the first, he states that in 1850 Rayer inoculated sheep with the blood of others dead with anthrax, and in this way transmitted the disease. It seems that Rayer published a short note of this work in *Bulletins de la Société de Biologie* in 1850, but we have not had access to this publication. Davaine's own work was of great value. Probably the most important experiments that he made were those in which he demonstrated that

the blood of an animal sick with anthrax is not capable of transmitting the infection to others unless it contains the germ. It may be of interest to briefly describe the experiments which led to the establishment of this fact. Rabbit A was inoculated with anthrax blood. Forty-six hours after inoculation, examination showed no micro-organisms in the blood of A. At that time twelve or fifteen drops of blood was taken from the ear of this animal and injected into Rabbit B. Nine hours later the blood of A was re-examined and found to contain a large number of bacteria. Then a few drops of blood was again taken from its ear and injected subcutaneously into Rabbit C. One hour after the last operation A died, and twenty hours later C died, while B remained free from infection. Space will not permit us to follow the literature of anthrax, except in so far as it refers to the chemical toxin, any further. Pasteur, De Bary, Bollinger, Koch, and others studied the morphology and life history of anthrax bacilli, and in doing so opened up the science of bacteriology. The reader is refered to the theories of the action of anthrax to the works of Bollinger,[9] Szpilman,[10] Joffroy,[11] Toussaint,[12] and Nencki.[13]

It is believed that the anthrax bacillus produces a specific toxin to which the symptoms of the disease and death are due. As we shall see later, much time and energy have been expended in search for this specific toxin, and this paper consists of the record of investiga tions undertaken for the purpose of determining whether or not a chemical poison is produced by the anthrax germ, and if so what are its origin and properties. In 1877 Pasteur[14] filtered anthrax cultures and also the blood of animals sick with this disease through porcelain and injected the germ-free filtrate into animals without inducing the disease, and concluded that this bacillus does not produce any soluble poison. We are of the opinion that subsequent investigations have established the correctness of the conclusions reached by Pasteur. However, there have been several claims to the discovery of soluble poisons in cultures of the anthrax bacillus and in the body of animals dead with this disease, and we will now proceed to briefly review some of these claims.

Hoffa[15] obtained from pure cultures of the anthrax bacillus small quantities of a substance which he believed to be a ptomain and the specific poison of this disease. When injected under the skin of

certain animals it was found to at first increase respiration and the action of the heart. After a short period the respirations were found to become deep, slow, and irregular. Later it was observed that the temperature fell below the normal, the pupils were dilated, and a bloody diarrhea set in. Postmortem examination showed the heart to be in systole, the blood dark, and ecchymoses were found on the pericardium and peritoneum. Subsequently, Hoffa believed that he had succeeded in isolating this substance from the bodies of animals dead from anthrax. He gave to it the name anthracin, and undoubtedly convinced himself that he had discovered the specific poison of this disease. No subsequent investigator—and several have repeated the experiments—has been able to fully confirm Hoffa's results, and it is more than likely that the poison which he found resulted from the action of the agents used in its detection and separation upon the constituents of the culture medium.

In 1889 Hankin[16] grew the anthrax bacillus in a medium consisting of Liebig's meat extract to which fibrin had been added; and from the filtrate of a culture of this kind, he precipitated with ammonium sulphate an albumose which, while not directly poisonous to animals, when injected simultaneously with an inoculation of the anthrax bacillus causes more speedy death than when the bacillus only was used. It was concluded from these observations that the albumose destroys the natural resistance of the animal to the disease, after which the bacillus is able to continue the elaboration of its poison in the animal body.

Petermann[17] has repeated Hankin's experiments and obtained an albumose which elevates the temperature from 1° to 2°, but is otherwise without poisonous effects, and without protective influence against the anthrax bacillus. Hankin and Wesbrook have repeated and modified the experiments of the former, and have reached the following conclusions: 1. The anthrax bacillus produces a proteolytic diastase by means of which albumoses may be formed from proteid material, but these albumoses have no immunizing action. 2. The anthrax bacillus produces another albumose. The production of this is by the direct action of the germ and without the intervention of the diastase. 3. We have been able to obtain this albumose in a relatively pure condition, that is to say, without mixture with the albumoses of digestion. This is accomplished by growing the bacil-

lus in a solution of pure peptone. 4. This albumose in very small doses confers upon mice partial immunity to anthrax. 5. This albumose in ordinary doses does not produce any poisonous symptoms in animals susceptible to anthrax. 6. Those animals which are relatively immune to anthrax, such as the rat and frog, are easily poisoned by this albumose. 7. On the contrary, young rats, which are susceptible to anthrax, are not poisoned by this substance.

Klemperer[19] obtained from cultures of the anthrax bacillus a substance which caused elevation of temperature, but which was not submitted to further investigation.

Brieger and Fraenkel[20] endeavored to prepare a toxalbumin from the organs of animals dead with anthrax. They cut the tissue into fine pieces, rubbed up with water, allowed to stand for twelve hours in an ice box, and filtered through porcelain. The filtrate was concentrated in vacuo at 30° to one-third its volume, and after being acidified with a few drops of acetic acid, was treated with ten times its volume of absolute alcohol. The mixture was then allowed to stand for twelve hours longer in an ice box, after which the precipitate was collected on a filter, dissolved in a small volume of water, refiltered, reprecipitated with alcohol; this being repeated until a perfectly clear aqueous solution was obtained. The albumose was further purified by dialysis, and as thus obtained it was found to be freely soluble in water and to give the ordinary reactions for albumin. These investigators failed to make any satisfactory study of the substance obtained by them, and as we shall see later, the repetition of their experiments by others has led to negative results.

Marmier[21] attempted to isolate an anthrax toxin from cultures grown in the following mediums: water, 1000 grams; peptone, 40 grams; sodium chlorid, 15 grams; sodium phosphate, 0.5 grams; potassium phosphate, 0.2 grams; glycerin, 40 grams.

This fluid before inoculation was filtered through porcelain and then sterilized at 110°. The peptone used was obtained from the commercial preparation by the precipitation of the other proteids with ammonium sulphate and by removing the salt by dialysis. In this culture medium the anthrax bacillus, especially the sporeless variety, grew abundantly. In order to obtain the toxin the culture was filtered and saturated at ordinary room temperature with ammonium sulphate, which produced a more or less abundant precipitate.

This was allowed to stand for some hours and filtered, after which the precipitate was washed with a saturated solution of ammonium sulphate. Subsequently the precipitate was dissolved in water, freed from salts by dialysis, concentrated, feebly acidified with sulphuric acid, and precipitated with alcohol. The substance thus obtained was found to be soluble in water and in a 1 per cent. solution of phenol. It is said not to give any of the reactions of albumins, propeptones, or alkaloids, but since there is no mention of the reactions tested, and since precipitation with ammonium sulphate is a propeptone reaction, we must consider this statement as somewhat indefinite and possibly as misleading. There is absolutely no proof that the toxin thus obtained was pure, nor that it had its origin in the anthrax bacillus, or was due to the growth of this germ, inasmuch as control tests were not made.

Heim and Geiger[22] grew anthrax bacilli in eggs after the manner of Hueppe, extracted with alcohol, precipitated the alcoholic extract with mercuric chlorid, filtered, treated the filtrate with platinum chlorid, decomposed the precipitate thus obtained with hydrogen sulphid, filtered, rendered alkaline with potassium hydrate, and divided into two portions, one of which was extracted with ether and the other with benzol. The amount of material removed with ether was small, but that obtained in the benzol extract was larger. When either of these residues was taken up in a few cubic centimeters of feebly acidified water and injected intra-abdominally into mice it caused salivation and lacrymation, followed by muscular convulsions and death. The smallest dose of the benzol extract which proved to be fatal was 0.5 c.c., while a similar amount of the ether extract caused only transient symptoms. Apparently no controls were examined by these investigators and the evidence that they obtained the specific toxin of anthrax is too slight to deserve serious consideration.

Iwanow[23] has demonstrated the presence of certain volatile acids, formic, acetic, and caproic, in anthrax cultures, but there is no evidence that the production of these bodies has anything to do with the pathology of the disease. Moreover, these acids are produced by a large number of bacteria, some of which are pathogenic, while others are not.

Petri and Massen[24] detected hydrogen sulphid in anthrax cultures, but inasmuch as at the same time they found this gas in every

one of the cultures of thirty-six other pathogenic germs, it cannot be said to possess any specific importance. Moreover, spectroscopic examination of anthrax blood fails to show the presence of hydrogen sulphid or any of its compounds, and there is no evidence that this gas has anything to do with the production of the disease.

Fermi[25] has shown the presence of both diastatic and peptonizing ferments in anthrax cultures, but these enzymes are common products of many bacteria, and in our study of the specific toxin they may be neglected.

Maumus[26] has shown that when the anthrax bacillus is grown on potatoes it converts an appreciable amount of the starch into glucose.

Roger[27] has shown that the anthrax bacillus secretes a ferment which coagulates casein.

Klein[28] removed the germs from agar cultures of forty-eight hours' growth, placed the same in 5 c.c. of bouillon, and after the tube had been held for five minutes in boiling water, injected its contents into the peritoneal cavity of a guinea-pig without results. Each animal received two-thirds of a culture. After a few days the injection was repeated and four or five days later these animals were inoculated intraperitoneally or subcutaneously with small doses of living cultures. All died within forty-eight hours of typical anthrax. From these experiments, Klein concludes that the anthrax bacillus does not form any intracellular poison, and that treatment with the substance of the cells confers no immunity to guinea-pigs.

Conradi[29] has endeavored to solve the question of the existence of an anthrax toxin by the following methods:

1. Guinea-pigs were inoculated intraperitoneally with anthrax, and immediately after death the peritoneal fluid, which varied in amount in different individuals, but averaged from 10 to 15 c.c., and contained in each field from 10 to 20 micro-organisms, was filtered through porcelain. In some of the experiments the filter of Chamberland was employed while in others that of Kitasato was used. The filtered peritoneal exudate was injected into mice, rats, and guinea-pigs subcutaneously, intravenously, and intraperitoneally, and always without effect. The amounts of the filtered exudate injected into mice varied from 2 to 4 c.c.; that into rats from 5 to 12 c.c.; in guinea-pigs from 4 to 15 c.c.; in rabbits from 10 to 20 c.c.; and in one dog, 25 c.c. was in-

jected subcutaneously. In proportion to body weight the mice received by far the larger injections. These experiments indicate that in the peritoneal exudate of guinea-pigs inoculated with anthrax there is no appreciable amount of soluble toxin.

2. Many guinea-pigs were inoculated with anthrax, and directly after death their livers and spleens were removed under aseptic conditions and rubbed up in a sterilized mortar with sterile sand to which a little physiologic salt solution had been added. After thorough rubbing the mixture was diluted with physiologic salt solution and filtered through a Chamberland tube under four atmospheres of pressure. The filtrate was injected subcutaneously, intravenously, and intraperitoneally into mice, rats, guinea-pigs, and rabbits, and in every case without effect.

3. Conradi, finding the preparation of collodion sacs difficult, substituted for them the vegetable membranes from *phragmites communis*, first used by Podbelsky.[30] (To one experienced in the preparation of collodion sacs this must be regarded as a clumsy substitution.) These sacs after sterilization were filled with bouillon cultures of the anthrax bacillus, and after laparotomy under ether were placed in the abdominal cavities of animals. The animals used were guinea-pigs, rabbits, and dogs, all of which remained well, notwithstanding the presence of these tubes containing virulent cultures of the anthrax bacillus in their abdominal cavities. These experiments satisfied Conradi that the anthrax bacillus does not produce any soluble toxin, and he next turned his attention to determining whether or not this organism possesses any intracellular poison.

4. The anthrax exudates obtained as described in the first series, in quantities of from 5 to 6 c.c., were placed in test-tubes, ½ c.c. of toluol added to each, the tube closed with a sterilized cork, thoroughly shaken, and then allowed to stand for ten days in the dark at room temperature. At the expiration of this time the contents of many tubes were placed in a separator and the toluol removed. Having shown by inoculation that the germ contained in these tubes was dead, the exudate thus sterilized was injected into susceptible animals subcutaneously without effect.

5. Asporogenous cultures were sterilized by exposure for 110 hours to —16°. After exposure to this temperature, the tubes were kept in an incubator at 20°, long enough to see that they remained

sterile, after which they were injected subcutaneously into susceptible animals, and always without effect.

6. A number of rabbits and guinea-pigs were simultaneously infected with anthrax, and after death the livers and spleens were subjected to a hydraulic pressure of 500 atmospheres. The fluid thus obtained, which on microscopic examination showed the presence of bacteria, was passed through a Chamberland filter, and then injected subcutaneously, intraperitoneally, and intravenously into mice, rats, guinea-pigs and rabbits, and always without effect.

7. The experiment of Brieger and Fraenkel in which they prepared their anthrax toxalbumin was repeated with negative results.

From these experiments Conradi reaches the following conclusions: "By no method known at present can it be shown that the anthrax bacillus forms either an extracellular or an intracellular poison within the bodies of either susceptible or insusceptible animals. Indeed these experiments increase the probability that the anthrax bacillus does not form any poisonous substance, therefore the solution of the manner in which anthrax infection results remains unknown. Whether improved chemical methods will lead to its detection or not cannot be determined, but for the present the anthrax bacillus at least must be regarded as a purely infectious micro-organism." If this conclusion reached by Conradi be true, the mechanical interference theory is the best that can at present be offered so far as anthrax is concerned.

We are now ready to report our investigations in the search for the anthrax toxin. Up to the present time we have not grown the anthrax bacillus in the large tanks which have been used in obtaining the large quantities of colon and other bacilli. Our anthrax germ has always been grown in Roux flasks, for the reason that the tanks have been in constant use in growing other germs. The first experiment made with anthrax was done incidentally to the study of the colon germ in May, 1900. An extract from our protocol of that date reads as follows: "Took the anthrax germs from twelve Roux flasks, placed the germ mass in a liter of 1 per cent. sulphuric acid, and kept in the incubator at 37° for twenty-four hours. At the end of this time, culture experiments demonstrated that the germ was still alive. The beaker containing the germ mass and the 1 per cent. sulphuric acid was placed in the autoclave and heated for thirty

minutes at 100°. Subsequent inoculations showed that this procedure had rendered the preparation sterile. It was then passed through a Chamberland filter under pressure, and the clear filtrate was poured into twice its volume of absolute alcohol, which formed a white flocculent precipitate. This precipitate was collected on a filter, washed with alcohol until the washings no longer gave an acid reaction, and then dried over caustic potash in vacuo. This substance is not colored when heated with nitric acid alone, but on the further addition of ammonia it develops beautifully the characteristic orange of the xanthroproteic test. It does not give either the biuret or the Adamkiewicz test in a satisfactory manner.

On May 21, 1900, an unweighed amount of this alcohol precipitate was dissolved in water and injected into the abdominal cavity of a guinea-pig. On the next morning this animal was found dead. Postmortem examination showed the heart in partial diastole, with clots in both auricles and ventricles. The peritoneal cavity contained a few cubic centimeters of a clear fluid.

At 4.45 P.M. May 22d a guinea-pig received intra-abdominally 60 mg. of the alcoholic precipitate dissolved in 5 c.c. of water. At 9.45 on the same evening this animal was apparently dying, and at 6.30 the next morning it was found dead. Postmortem examination showed a condition identical with that found in the preceding pig. Cultures from the heart's blood remained sterile.

At that time we did not appreciate the value of these experiments, and it was not until it had been shown by work in this laboratory that a toxin could be split off from the colon germ with dilute acid that we thought of returning to our studies of the anthrax toxin, because the facts that had been ascertained concerning the nature of the colon toxin were in accord with the above recorded results obtained with the anthrax bacillus.

On February 4, 1902, a guinea-pig of 400 grams' weight was treated subcutaneously with $\frac{1}{2}$ c.c. of a bouillon culture of anthrax twenty-four hours old. This animal died on February 7th, and one drop of the blood from its heart was added to a tube of beef-tea, and 1 c.c. of this was injected subcutaneously into a second pig. This animal died within forty-eight hours, and a culture made from the heart blood of this animal was injected subcutaneously into a third pig, which also died within forty-eight hours. With the heart blood

of this third animal two flasks of beef tea were inoculated and kept in the incubator at 37° for twenty-four hours, when from 2 to 3 c.c. of this beef-tea culture was added to each of twenty Roux flasks containing 2 per cent. of agar. Care was taken to see that the beef-tea culture of the anthrax germ was well distributed over the surface of the agar in the Roux flasks. These flasks were then kept in the incubator at 37° for six days, when the germ substance was scraped off the surface of the agar by means of sterilized bent glass rods, and placed in one liter of a 1 per cent. solution of sulphuric acid. Care should be exercised in removing anthrax germs from Roux flasks, and we have found it convenient to do this over a large shallow tray containing a 5 per cent. solution of lysol. The cotton is withdrawn from the flask, 15 or 20 c.c. of the dilute acid is poured in, and by means of a bent glass rod the germ growth is carefully separated from the agar, broken up into a suspension and poured into a beaker. The germ mass thoroughly mixed with the 1 per cent. sulphuric acid was heated for two hours on each of two consecutive days on a water bath. After the second heating it was filtered through hard paper, and the filtrate proved to be perfectly clear and free from suspended matter. The filtrate thus obtained was poured into five volumes of alcohol, and an abundant flocculent precipitate immediately formed. After subsidence, this precipitate was collected upon a filter, washed with alcohol until the washings no longer gave an acid reaction, then redissolved in water and reprecipitated by pouring the aqueous solution into five volumes of alcohol. After this the precipitate was collected upon a filter-paper, washed with alcohol, and dried in vacuo over potash. After drying, the precipitate was rubbed up in an agate mortar, and after thorough pulverization was again placed in vacuo for the purpose of completing the drying process.

The dilute acid extract, obtained as described above, from the anthrax bacillus, was injected intra-abdominally into three guinea-pigs, one receiving 100 mg., another 60 mg., and a third 20 mg. None of these animals was affected by this treatment, and it was quite evident that there was a direct contradiction between the results obtained in the experiments made in 1900 and those just detailed. The reason for the non-poisonous action of the sulphuric acid extract as prepared in the last described experiments was not difficult to find.

As has already been stated, the germ mass had been heated for two hours on each of two consecutive days at the temperature of the water bath with dilute acid, and the most probable explanation of the difference in the result was that this prolonged heating had destroyed the toxin.

Fifty-two flasks of agar were inoculated in the same manner as previously described, and allowed to grow in the incubator at 37° for eight days. At the expiration of this time the germ substance from twelve of these flasks was taken up with 1 per cent. sulphuric acid by weight, and this suspension was heated in the autoclave at 110° for exactly ten minutes. Inoculation experiments showed that this treatment rendered the mixture sterile. The preparation was then filtered through hard paper, and furnished a perfectly clear, transparent filtrate. This filtrate was slowly poured, with constant stirring, into three volumes of 96 per cent. alcohol. A somewhat voluminous, flocculent precipitate formed. This was allowed to subside during the night, and the next day it was collected upon a filter-paper, washed with alcohol until the filtrate ceased to give an acid reaction, redissolved in water, and reprecipitated with alcohol, and then dried in vacuo over caustic potash. After drying it was pulverized in an agate mortar, and was used upon animals in the following manner:

An unweighed portion of this powder was dissolved in 5 c.c. of water, rendered feebly alkaline with sodium hydrate, and injected at 2.50 P.M. into a guinea-pig weighing 122 grams. The pig seemed to be very sick throughout the afternoon, and up to 12 P.M. Its breathing was irregular and difficult. At 6.30 A.M. the next day the animal was found dead. Postmortem examination showed extensive subcutaneous edema over the abdomen. The peritoneal cavity contained a few c.c. of clear fluid, and a smaller amount of a bloody exudate was found in the pleural cavity. The heart was in diastole, and the most marked changes were found in the lungs. These were greatly congested, and the left upper lobe seemed to be consolidated. The kidneys were highly congested, and the liver seemed pale and friable. Closer examination of the lungs showed portions of it to be completely hepatized. Many of the air cells were filled with exudate and blood corpuscles.

Fifty mg. of this powder dissolved in 5 c.c. of feebly alkaline water was injected into the abdominal cavity of a guinea-pig weighing 237

grams at 11.30 A.M. During the day this animal suffered from irregular breathing, and died at 6 P.M. Postmortem examination showed extensive subcutaneous edema over the abdomen, some fluid in the peritoneal cavity, but none in the pleural. The lungs were congested, but not so markedly as in the preceding case. The kidneys were highly congested, and bled freely on section. The suprarenals were normal in appearance.

This toxin, which is split off from the anthrax bacillus by dilute sulphuric acid, loses its toxicity when heated for a long time in water, as the following experiment will show:

One hundred mg. of the powder used in the preceding experiment was dissolved in 5 c.c. of feebly alkaline water, and boiled for ten minutes over the naked flame in the test-tube, after which it was injected intra-abdominally into a guinea-pig weighing 207 grams, at 3.50 P.M., April 15, 1902. During the next twelve hours this animal manifested the same symptoms as seen in those treated with the toxin which had not been heated for so long a time, but on the next morning it had apparently recovered. However, it was found dead on the morning of April 18th. Postmortem examination failed to reveal any of the lesions seen in the other pigs poisoned with this toxin, and, unfortunately, no culture from the heart's blood was made. It is therefore doubtful whether or not this animal died from the effects of the material injected.

Fifty mg. of the toxin split off from the anthrax bacillus with dilute sulphuric acid seems to be about the minimum amount which is fatal to guinea-pigs of 200 grams' body weight. Two pigs, weighing 259 and 247 grams, were treated intra-abdominally, respectively, with 25 and 15 mg. of this toxin. Both were seriously sick for some hours, but ultimately recovered.

Next we endeavored to ascertain whether or not the entire germ substance has any toxic action. With this in view the following experiment was conducted: The germ substance from thirty Roux flasks was removed with 96 per cent. alcohol, and autoclaved at 120° for twenty minutes. Cultures from this suspension remained sterile. After standing for three days the mixture was filtered and fresh alcohol added to the germ substance. This was allowed to stand for twenty-four hours longer, and, inasmuch as the alcohol no longer became colored on being agitated with the germ substance, the latter

was collected upon a filter-paper, washed thoroughly with alcohol, and then with ether. The germ substance thus obtained was dried, first between folds of filter-paper, then in vacuo over calcium chlorid. After being dried, it was placed in a mortar and pulverized, and in this way we obtained a large amount of a grayish-white powder, which, when stained and examined under the microscope showed the germs appearing typically, but more or less broken. Portions of 50, 75, 100 and 150 mg. of this substance suspended in 5 c.c. of water and heated, in order to ensure sterilization, and injected into the abdominal cavities of guinea-pigs failed to kill, but all showed marked symptoms of sickness, and these varied in intensity in direct proportion to the amount of the germ substance given. Larger doses, and especially quantities of from 200 to 225 mg., suspended in water, heated, and injected directly into the abdominal cavities of guinea-pigs, cause death within from twelve to twenty-four hours. The following experiment illustrates these statements:

Two hundred and twenty-five mg. of the germ substance suspended in water, and after being boiled was injected intra-abdominally into a guinea-pig weighing 340 grams at 3.25 P.M., April 24th. The animal was found dead at 8.30 A.M., April 25th. There was extensive subcutaneous edema over the abdomen, and from 10 to 15 c.c. of fluid in the peritoneal cavity. The bloodvessels of the mesentery and the peritoneal coat of the intestines were slightly congested. A considerable amount of the germ substance remained undissolved in the peritoneal cavity. The lungs appeared to be normal; the heart in partial diastole, and a culture from the heart's blood remained sterile.

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PART IX.—CONCLUSIONS.

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The work detailed in this report leads me to the following conclusions, subject to such modifications as may be rendered necessary by more exhaustive researches:

The dead cells of each of the micro-organisms studied, both the pathogenic and the non-pathogenic, are poisonous to guinea-pigs and rabbits. The intracellular toxin of a non-pathogenic germ may be more potent than that of a highly infectious organism. The

minimum lethal dose of the air-dried cells of the micrococcus prodigiosus for a guinea-pig of from 200 to 300 g. weight is 3 mg., while that of the anthrax bacillus for the same animal is about 200 mg. Even the lemon sarcine, the least toxic of the non-pathogenic micro-organisms examined, surpasses the anthrax bacillus in the potency of its intracellular toxin. These facts indicate that the intensity of the infectious properties of a micro-organism is not always at least measured by the potency of its toxin. The prodigiosus is non-pathogenic to the higher animals, not from its inability to elaborate a toxin, but because it cannot grow and multiply in the animal body; while, on the other hand, the anthrax bacillus is highly infectious to some of the higher animals, not from the intensity of the poison which it elaborates, but rather from the fact that in these animals this germ finds the conditions favorable to its growth and multiplication.

The chief constituent of the bacterial cell is a glyconucleoproteid; and by this term I do not mean a mixture of carbohydrate, nuclein and proteid, but a molecule containing atomic groups which when split off from the molecule belong to these chemical divisions. Since there are at least in some of these cells two carbohydrates, it is probable that only one of these exists as a constituent of the complex molecule, while the second may serve as reserve food material. It is also probable that there are traces of proteid besides that which forms part of the glyconucleoproteid. Further work must be done before we can speak with authority concerning the nature of the proteid group or groups in the complex molecule. A satisfactory solution of the question of the existence of a protamin group in the complex molecule will be of much value to our knowledge of cellular chemistry in general. From the work done so far I am inclined to the opinion that there is a protamin-like group, but that we shall find that these bodies differ quite markedly from the protamins which have been obtained from the spermatozoa of fish. This opinion is founded upon the difference in behavior of the bodies split off from bacterial cells by dilute acids from the protamins obtained in like manner from fish spermatozoa. Especially is this difference marked in the failure of the former to give a satisfactory response to the biuret test.

The intracellular toxins studied in these researches are not contained as such in the cells, but are atomic groups or side chains of

the complex molecule. This statement is founded upon the observation that the toxin can be detached from the cell substance only by the action of agents which break up the complex molecule. Mere solvents, such as water, alcohol, ether, saline solutions, and glycerin, do not remove the toxin from the cell, but when the bacterial substance is acted upon by some hydrolytic agent, such as dilute sulphuric acid, a toxin is detached and passes into solution. However, the cell substance does not lose all of its toxicity when treated with dilute acid. In my opinion, this indicates that the complex molecule contains two or more toxic groups or side chains, only one of which is split off by dilute acid. Furthermore, it has been shown in these studies that after one thorough extraction of the cell substance with dilute acid, subsequent treatment of the residue with the same agent is without effect, or at least does not result in the splitting off of more toxin. This indicates that there is a definite and certain atomic group or side chain which can be obtained by hydrolysis. Our experiments, especially with the colon and anthrax bacilli, have furthermore shown that prolonged hydrolysis of the toxin split off by dilute acid furthermore changes it, inasmuch as such treatment robs it of its toxic property. The readiness with which this toxic group is split off from the cell substance probably differs greatly in different species and possibly even in the same germ under different conditions of growth. Our studies of the toxins of the diphtheria bacillus are most suggestive in this connection. The most reasonable explanation of the facts observed in our researches on the toxins of diphtheria is the following: All the toxins of the diphtheria bacillus are of intracellular origin, or are atomic groups of the complex molecule which constitutes the most important part of this organism. One of these toxic side chains is easily split off from the parent molecule. This separation occurs in the growth of the organism, and the water of the culture medium is the hydrolytic agent. The solution of this group constitutes the ordinary diphtheria toxin, which is used in the immunization of horses and the preparation of diphtheria antitoxin.

This being a detached side chain from one molecule, we can easily understand how, as suggested by Ehrlich's theory, it readily attaches itself to some complex molecule in certain cells in the animal body. But by this combination, this molecule, whose normal function is to build up and feed the cell by combining with nutritive bodies, is

rendered worthless to the cell, and is cast out and another molecule formed. The continued introduction of the toxin in small amounts leads to the elaboration of other molecules, and finally these are formed and cast out from the cell more rapidly than they are combined with the toxin, and thus these molecules come to make up the antitoxin of the blood serum. That the diphtheria toxin consists of a simpler and smaller atomic group than the diphtheria antitoxin is indicated by two well-known observations: 1. The toxin filters through porcelain more readily than the antitoxin. 2. The toxin when injected into a bloodvessel speedily diffuses, and soon is found equally distributed in the blood and the lymph, while diphtheria antitoxin, when injected intravenously, diffuses from the blood into the lymph more slowly. Furthermore, Ehrlich has shown that diphtheria toxin decreases in toxicity on standing, just as we have found that our toxins split off by dilute acids decrease in toxicity by prolonged hydrolysis. Again, Ehrlich learned that notwithstanding the decrease in toxicity of the diphtheria toxin on standing, it requires just as much antitoxin to neutralize it as it originally did; just as we have found that notwithstanding the decrease in toxicity of our toxin split off with dilute acids on prolonged hydrolysis their behavior chemically is not altered. We also found that the bacterial cell contains a toxin group which is not neutralized by commercial antitoxin, thus furnishing additional proof that the complex molecule of the diphtheria cell contains at least two toxic groups. This is equally true of the colon bacillus, and affords an explanation of the fact observed by Metschnikoff, that animals immune to ordinary diphtheria toxin may not be immune to diphtheria infection. It is further possible that this may have something to do with the well-known fact that diphtheria antitoxin in order to be most serviceable clinically must be employed in the early stages of the disease. In the child's throat the diphtheria bacillus is growing practically on the outside of the body, and the first ill effects are due to the absorption of the easily detached toxic group. Later in the disease it is possible that other toxic groups are absorbed, and against these commercial antitoxin has no protective influence. This is offered only as a suggestion. However, the most interesting observation that we have made concerning the toxin of diphtheria is that the strain which produces a large amount of what some call the extracellular toxin, and which

is probably identical with that split off by hydrolysis, yields only a small amount of toxin detachable by dilute acid, while, on the other hand, a culture which yields only a small quantity of the former furnishes the latter more abundantly. This suggests that possibly germs of different strains may vary in the readiness with which the toxic group is detachable from the molecule. Can this have anything to do with attenuation? It is at least conceivable that of two varieties of the same organism the animal body would have a better chance of protecting itself from the one which cast off its toxins least readily. In this connection it is worthy of notice, that so far we have found in none of the non-pathogenic organisms a toxic group detachable by hydrolysis.

The nature of the toxins split off from the bacterial cells by means of dilute acids has not been thoroughly investigated. They seem to be of relatively simple composition. They give only the xanthoproteic among the color reactions, and the sulphates of those from the colon and anthrax bacilli yield practically the same per cent. of ash.

SPONTANEOUS NON-TUBERCULOUS PNEUMOTHORAX.

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OF PHILADELPHIA.

By spontaneous non-tuberculous pneumothorax we understand a pneumothorax occurring suddenly in healthy individuals, without the cause being discoverable by physical examination or by the history of the case, and in which there is rarely a formation of liquid.

Pneumothorax was probably known to the ancients, but no clear account has come down to us. It is true that Hippocrates mentions the succussion splash, but this was wrongly interpreted as meaning pus in the pleural cavity; while, in reality, it means the presence of both air and fluid. Apparently the first to appreciate the condition was Riolan, a contemporary of Harvey, although the first exact description of it was not given until a century ago, in 1803, by Itard,[1] a French physician, who coined the term pneumothorax. His studies were made in the postmortem chamber, and neither he nor his immediate successors seem to have recognized the condition during life. This was reserved for Laennec,[2] whose investigations, particularly of the symptoms and diagnosis of the disease, were so thorough that posterity has been able to add but little to them.

Laennec gave the probable causes of pneumothorax as: (1) tuberculosis; (2) decomposition of pleural effusions; (3) gangrene of the lung; (4) emphysema of the lung; (5) idiopathic formation of air in the pleural cavity. By the latter, Laennec understood a sort of gaseous secretion on the part of the pleura. The second and last of these causes were finally, in the light of many observations, put aside; although the second, decomposition of pleural effusions, has lately been revived on good evidence. Thus, Levy[3] reported a case in which it seemed beyond doubt that a pneumothorax had supervened on a

pyothorax, as the result of decomposition by an anaerobic organism, apparently the Bacillus aerogenes capsulatus.

May and Gebhardt[4] likewise reported a similar case of pneumothorax due, in this instance, to the Bacillus coli communis, and they proposed the name zymotic pneumothorax for one having such an origin. The Proteus vulgaris and other undetermined organisms have also been found in cases of this kind, particularly by French writers, who employ the term *pneumothorax par fermentation gazeuse.*

The most common cause of pneumothorax is tuberculosis; this is not alone the experience of individual observers, but is shown to be the fact by several series of statistics. Thus Biach,[5] in 1880, collected all the cases of pneumothorax which had occurred in three hospitals in Vienna: 918 cases had been observed, which were divided, according to their cause, as follows:

Tuberculosis	715 cases.	Bronchiectasis	10 cases.
Gangrene	65 "	Abscess of the lung	10 "
Empyema	45 "	Emphysema	7 "
Traumatism	32 "	Infarction	4 "
Echinococcus	1 "	Perforated esophagus	2 "
Thoracentesis	1 "	Abscess of the bronchial glands	2 "
Worms	1 "	Fractured ribs	1 "
Peritonitis	1 "	Fractured sternum	1 "
Ulcer of stomach	2 "	Uncertain	14 "

As regards the frequency with which pneumothorax occurs in pulmonary tuberculosis, the following statistics, quoted from Biach, are of interest: In 58,731 cases of tuberculosis which had been observed, 433—or less than 1 per cent.—developed pneumothorax. Galliard[6] found 36 instances of pneumothorax among 3415 cases of pulmonary tuberculosis, making a percentage of 1.054. These are smaller percentages than those found by Lebert and by West,[7] who give the frequency as 5 per cent. In 1000 cases of phthisis at the Brompton Hospital, there were (Fowler and Goodlee[8]) 65 cases of pneumothorax (6.5 per cent.).

It is seen from these statistics and from others which have been compiled that from 80 to 90 per cent. of the cases of pneumothorax are due to tuberculosis, while the proportion of tuberculous cases that develop pneumothorax is from 1 per cent. to 6.5 per cent. Among the uncertain cases (14) in the foregoing series, there are a few of the so-called spontaneous, idiopathic, or accidental pneumothorax.

When these spontaneous cases were first observed and reported, it was thought that they probably arose from a small tuberculous nodule which could not be recognized by physical examination or by the history. This view is apparently still held by some reporters—notably

by West,[9] Delafield (Case 52, our series), Talayrack,[10] and Hamilton.[11] West[12] says: "Experience and experiments seem to show that when pneumothorax has taken place in the apparently healthy, a lesion which may even be of a tuberculous character has really been the cause of the accident." Delafield apparently takes it for granted that his case was tuberculous, although neither physical examination nor the history of the case bears out this conclusion. Hamilton seems to have based his belief largely upon West's great experience. Cases have been observed, however, that have come to postmortem, which prove that in some instances, at least, tuberculosis is not present; as iu the cases of Ranking and Devillier (Nos. 9 and 1, our series). Two other cases, those of Chauffard and Osler (Nos. 40 and 48, our series), were treated by tuberculin, and gave no reaction. The authors have observed the two following cases, which are certainly cases of spontaneous pneumothorax, and which, they believe, are not tuberculous. The notes are copies of those made at the bedside of the patients.

CASE I.—Katherine G., aged twenty-one years; father and mother living; mother the subject of diabetes mellitus; father well. One sister dead of unknown cause. One sister and three brothers living and well. There is no tuberculosis in the family. When the patient was fifteen years of age she had a severe attack of chlorosis, from which she entirely recovered. When nineteen years old she gave birth to a perfectly healthy infant. (This child is living and well at present.) In 1894 she had a rather severe attack of dysentery. Except for the above conditions, she was perfectly well until March 14, 1895. On that date one of us (F.) was called to see her for some ill-defined ailment. A careful physical examination made at the time showed all the organs to be normal. On the morning of March 21, 1895, she was awakened from her night's sleep by a severe stabbing pain in the region of her left nipple, accompanied by distressing dyspnea. On inspection the left chest was seen to be without respiratory movement. It was distinctly distended. There was no tactile fremitus. There were no voice sounds or breath sounds heard over the left side. The apex-beat of the heart was in the fifth intercostal space on the right side of the chest. There was marked dulness on percussion. She received morphin and was kept in bed. On the next day there were the same physical signs, except that the dull note on percussion noticed over the left chest was found to be replaced by a resonant note.

The next day, March 23d, the note over the left chest was hyperresonant, and there was amphoric breathing over the base. On this

day the patient's temperature was normal. She still suffered considerably, and the chest was aspirated. Nothing but air was found. The heart at once resumed its normal position, and the patient speedily recovered. At the end of two weeks she was able to resume her usual duties. She has never been ill since. To-day, seven years after the attack of pneumothorax, she is perfectly well.

CASE II.—The patient, P. B., a teamster, aged twenty-seven years, born in Ireland, was admitted to the Philadelphia Hospital on December 16, 1901, in the service of Dr. S. Solis Cohen, through whose courtesy we are able to make this report. His sole complaints were cough and pain in the right side. The family history was exceptionally good. The parents, three brothers, and three sisters, were living and in good health. One sister had died in infancy. The man himself had had the diseases of childhood and typhoid pneumonia. As a teamster he always had been much exposed; he had also drunk considerably.

For a month prior to admission he had had, as the result of exposure, a cough, which did not trouble him greatly. The night before his entrance into the hospital he had a particularly violent fit of coughing, during which he was seized with severe pain in the right side. He had to go to bed, and the next day was brought to the hospital.

On admission he was found to be a tall, robust, well-nourished man, with a flushed and rather cyanotic face. The breath smelled strongly of alcohol. There was no dyspnea apparent. The chest was large and deep, the intercostal angle obtuse. The right side of the chest was larger than the left, and the intercostal spaces on the former side bulged slightly. Expansion was deficient over the entire chest, particularly upon the right side, on which the fremitus was also decidedly less than normal, especially toward the base. The right nipple was half an inch higher than the left, and on inspiration the intercostal spaces retracted less on the right than on the left side.

On percussion the note over the right side was more resonant than that over the left. At the right apex the note had a quality which could be designated wooden tympany; it was not a clearly tympanitic note. Toward the base, however, the percussion sounds were decidedly and characteristically tympanitic. The liver dulness was entirely obliterated. There was tympany at front, side, and back, down to the edge of the ribs; and the note here in the right hypochondrium, as has been stated, was more tympanitic than over the upper part of the chest. The differences in the percussion note, as well as other features, are shown in the accompanying diagram and photograph. The tympanitic sound extended beyond the left border of the sternum.

Auscultation. On the left side the breath sounds were feeble, the vesicular element being almost suppressed. Expiration could not be distinctly heard in all parts, but where detected was prolonged and

FIG. 1.

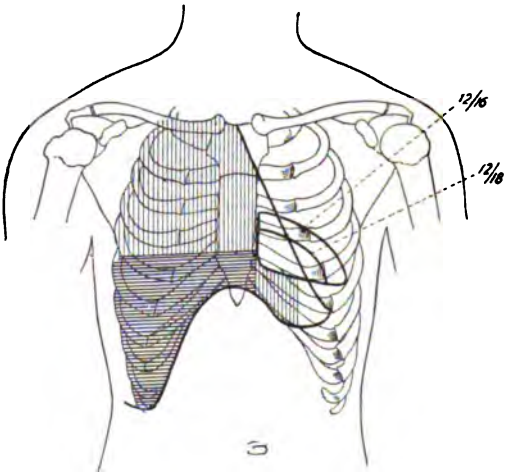
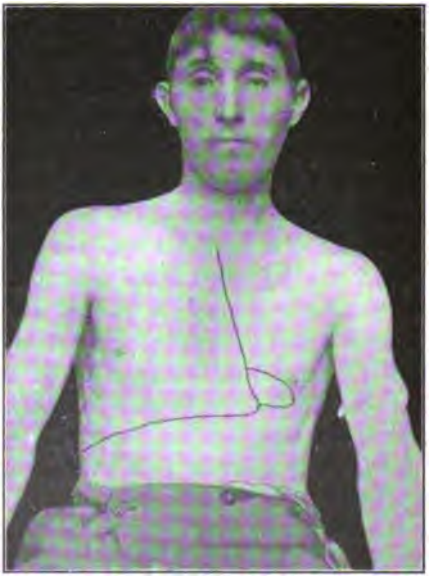


FIG. 2.



low-pitched. On the right side the breath sounds were entirely inaudible over the back. In the axillary region a distant breathing could be heard, the expiration being somewhat harsh. At the extreme apex in front the breath sounds were audible, but faint; below they were absent. Upon expiration an occasional sibilant râle could be heard. The vocal resonance was diminished, but not entirely absent.

The apex-beat was found in the fifth interspace, half an inch outside of the nipple line. The boundaries of the organ were not easily determined. They were on the right side of the left sternal border, above the third interspace; the left border was a finger's breadth outside of the nipple line; the lower at the sixth rib. There was some epigastric pulsation. The first sound was feeble at the base; the second pulmonic was accentuated. The apex sounds were feeble and distant.

On the following day, December 17th, the patient's condition was about the same, except that the cyanosis had increased and the apex-beat and the left heart boundary were a little further to the left than they had been. We strapped the patient's side, and this at once relieved the pain.

On the next day, December 18th, the patient, the notes say, was more comfortable; the cyanosis was less, there was some enlargement of the veins in the right hypochondrium, and the tympany still persisted. The heart, however, had receded fully an inch, the apex being now just within the nipple line, as is shown in the diagram.

On December 19th, three days after admission, an attempt was made to obtain the succussion splash, but without any result. There was evidently no fluid in the pleural cavity. The respiration on deep breathing was somewhat amphoric. The coin-test was tried, but did not yield a characteristic result. There was no bell tympany, although the sound on the diseased side was different from that on the healthy one, particularly just below the angle of the scapula.

Mensuration of the chest on this day showed an expansion of $\frac{5}{8}$ of an inch at the level of the axilla, and $1\frac{1}{4}$ inches at the nipple line. The circumference of the right side just below the axilla was $19\frac{1}{4}$ inches; that of the left, $17\frac{1}{2}$ inches; at the level of the nipples the right measured $19\frac{1}{4}$ inches; left, $17\frac{1}{2}$ inches; at the level of the ensiform cartilage, right side, $18\frac{1}{2}$ inches; left, $17\frac{1}{2}$ inches.

The urine was acid in reaction and had a specific gravity of 1012. It was free from albumin and sugar, but the sediment contained a few hyaline casts, triple phosphates, and epithelial cells. The sputum was also examined; it contained no tubercle bacilli. Fever was absent throughout.

The patient rapidly improved, and on December 23d, a week after admission, requested his discharge. The signs of pneumothorax were still in part present, and the cyanosis had not entirely disappeared, but there was no cough and no distress. He was seen three months afterward, and was entirely well, the breath sounds being normal and equal over both lungs.

It will be observed that in these two cases a pneumothorax appeared suddenly; in one of them during sleep. In neither of the cases were there any physical signs, symptoms, or history which would warrant a diagnosis of tuberculosis. In both of them recovery was complete. In one of the cases aspiration was resorted to for relief of the symptoms.

In a rather careful search through the literature of pneumothorax we have been able to collect 56 cases which appear to belong to the class of spontaneous non-tuberculous pneumothorax.

An analysis of the tables show the following facts:

List of Cases.

Reporter.	Sex and age.	Side affect'd	Duration.	Cause.	Symptoms.	Treatment.	Result.
1. Devillier. Thèse, Paris, 1826.	M. 18	Right	Several days.	.....	Dyspnea; pain.	None.	Death.
2. Ferrari. Gaz. Méd. de Paris, 1856, No. 11.	M. 16	Right	Few days.	Over-exertion.	Resonance over chest, pain, dyspnea, fever, cyanosis, no respiratory sounds, distention of chest.	Aspiration.	Recovery.
3. Brunnicke. Dublin Hospital Gazette, 1856, p. 111.	M. 31	Right	Few weeks.	.....	Perfectly well three months after.	.....	Recovery.
4. Dowell. Ibid., September, 1856.	M. 28	Left	3 to 4 weeks.	Severe cough.	Pain; slight cough.	.....	Recovery.
5. Thorburn. British Medical Journal, 1860, vol. i. p. 413.	M. 32	Right	2 mos.	24 hours after hard rowing.	Few; only dyspnea, resonance, metallic tinkling, amphoric breathing.	Rest; iodine externally.	Recovery.
6. Thorburn. Ibid.	M. 37	Right	2 mos.	After gardening.	Same as above.	Rest.	Recovery.
7. Wipham. Proc. London Med. Soc., vol. ix. p. 247.	M. 31	Right	1 mo.	No exertion; had been sitting in draught.	Pale, anxious; amphoric breathing; metallic voice sounds; resonance on percussion good; fremitus.	Rest.	Recovery.
8. Ricker. Wien. med. Woch., 1860, No. 28.	M. 18	Left	2 mos.	During coughing	Pain; dyspnea.	Aspiration; patient relieved at once.	Recovery.
9. Ranking. Ranking's Digest, 1860, No. 11, p. 96.	M. 19	Left	2 mos.	.....	Pain, dyspnea, distention of side, dislocation of heart, amphoric breathing; metallic tinkling.	No treatment.	Recovery.
10. Abeille. Gaz. Méd. de Paris, 1867, No. 1.	M. 29	Right	7 wks.	Hard work.	Pain, dyspnea, no phys. signs at first, three days later amphoric breathing, tympany, metallic tinkling.	Morphin for pain; rest.	Complete recovery.
11. Vogel. Deutsch. Arch. f. klin. Med., 1867, vol. xi. p. 244.	F. 29	Right	4 wks.	Over-exertion.	Pain, dyspnea, dislocation of heart.	Opium; rest.	Recovery.
12. Rilliet and Barthez. Maladies des Enfants, vol. i. p. 614. Quoted by Galliard.	... 3	Right	30 dys.	Unknown.	Pain, dyspnea, amphoric breathing; no metallic tinkling.	.....	Recovery.
13. Oppolzer. Allg. Wien. Med. Zeit., 1868, No. 52.	M. 17	.....	Few days.	.....	Sharp pain, dyspnea, dislocation of organs, resonance, bell tympany.	Opium; rest.	Recovery.
14. Forster. Archiv f. klin. Med., 1869, vol. v. p. 545.	M. 28	Right	3½ mos.	During walking.	Pain, dyspnea, tympanitic dulness, metallic tinkle, breath sounds weak, distention of side.	Morphin for pain; rest.	Recovery.
15. Mackenzie. Lancet, Aug. 19, 1871.	M. 50	Right	3 wks.	Exertion.	Pain, dyspnea, lividity, amphoric breathing, metallic tinkling; well in a few days.	Aspiration.	Recovery.
16. Wilks. Brit. Med. Journ., 1874, p. 770.	M. y'ng	Left	Few days.	Exertion.	Sudden onset, gasping, pain, tympany over chest.	None.	Recovery.
17. Wilks. Ibid.	M. eld'ly	.....	Few days.	Exertion.	Intense dyspnea.	None.	Recovery.
18. Wilks. Ibid.	F. 30	Left	3 mos.	Walking.	Eight months pregn't, delivered at term; dyspnea, cough; no breath sounds, no voice sounds.	Aspiration.	Recovery.

Reporter.	Sex and age.	Side affect'd	Duration.	Cause.	Symptoms.	Treatment.	Result.
19. Church. Edinburgh Med. Journ., June, 1875.	M. 39	Right	3 wks.	Walking.	Pain, dyspnea.	Aspiration.	Recovery.
20. Bossasinsky. Canst. Jahr., 1876, vol. xi. p. 168.	M. 30	.....	26 dys.	.....	Attack occurred during sleep.	.....	Recovery.
21. Bull. Ibid., 1877, vol. xi., p. 171. Quoted by Biach.	F. 29	Left	Short time.	Playing, inst. conversation.	Two attacks, one after playing piano, another after talking.	.....	Recovery from both attacks.
22. Heitler. Wien. med. Woch., 1879, No. 17.	M. adult	Right	2 mos.	While dressing.	Dyspnea, no fever; tympany, distention of side; heart in normal position?	.....	Recovery.
23. Delgrange. Journ. des Sci. Méd. de Lille, in Brit. Med. Journ., 1881, p. 196.	M. 18	Left	8 dys.	Inflating chest.	Pain, dyspnea.	.....	Recovery.
24. Fraentzel. Ziemssen's Encycl., vol. iv. p. 746.	M. 19	.....	6 wks.	Rolling barrel.	Tearing in chest; dyspnea.	.....	Recovery.
25. Biermer. Würzburger Med. Zeit., vol. i. p. 385.	M. 18	Left	7 wks.	Dancing.	Sensation of oppression, dizziness.	Some liquid formed.	Recovery.
26. Flint. Practice of Medicine, 1881.	M. 29	Left	7 wks.	Carrying a pack.	Pain, tympany, dyspnea, amphoric breathing, metallic tinkling.	Morphin.	Recovery.
27. Johnson. Clin. Soc. Trs., 1882, p. 159.	M. 17	Left	2 mos.	Playing.	Pain, dislocation of viscera three days after onset of pain.	Rest.	Recovery.
28. Rix. Quoted by Hall.	M. 39	Left	7 wks.	While sweeping.	Pain, faintness, hyperresonance, metallic tinkling, no cough.	None.	Recovery.
29. West. Clin. Soc. Trans., 1884, p. 56.	M. 24	Right	5 wks.	?	Pain, dyspnea, displaced heart and liver, bell tympany, amphoric breathing, metallic tinkling.	Aspiration.	Recovery.
30. Symonds. New York Med. Record, 1886, vol. i.	M. adult	Left	8 wks.	Riveting.	Pain, dyspnea, dislocation of organs, no respiratory murmur.	None.	Recovery.
31. Vinay. Lyon. Méd., Jan. 30, 1887.	M. 19	Left	2 mos.	?	Pain, no movement on affected side, no fremitus; tympany, amphoric breathing, metallic tinkling, dislocation of heart.	Morphin for pain.	Recovery.
32. Hall. Clin. Soc. Trans., 1887, vol. xx.	M. 24	Left	1 mo.	Unknown.	Temp. 100°, resonance, metallic tinkling; a second attack with no apparent cause.	Quiet.	Recovery.
33. Galliard. La France Méd., 1887, vol. iii. p. 1617.	M. 33	Right	Short time.	Exertion.	Pain, tympany, no fremitus, silence over chest.	Rest.	Recovery.
34. Gabb. British Med. Journ., 1888, vol. xi. p. 178.	F. 56	Right	Each attack 2 or 3 months	Strain.	Pain, dyspnea, amphoric breathing, at first low down, later above resonance; four attacks well recorded, 1874, 1880, 1882, 1888.	Morphin.	Recovery
35. Waller. Lancet, 1890, vol. i.	M. 16	Right	2 mos.	Jumping.	Pain, faint breath sounds, slight fever, slight dulness.	Tapped, with instant relief.	Recovery.
36. Lundie. Edinburgh Med. Journ., 1891, p. 220.	M. 20	Left	1 mo.	Thinks an old pleural adhesion torn.	Pain, dyspnea, hyperresonance, no heart dulness, no breath sounds, heart was dislocated backward.	None.	Recovery.

Reporter.	Sex and age.	Side affect'd	Duration.	Cause.	Symptoms.	Treatment.	Result.
37. Glaeser. Zeit. f. klin. Med., 1892, p. 394.	M. 32	Left	1 mo.	Unknown.	Sudden onset, dyspnea, pain, tympany.	Tapped, with instant relief.	Recovery.
38. Klemperer. Deutsche med. Woch., 1893, p. 602.	M. 21	Left	2½ wks	Screaming.	Pain, dyspnea, unconsciousness, cyanosis, no breath sounds; dislocation of viscera.	Rest; opium.	Recovery.
39. Galliard and Barbe. Gaz. des hôp. de Paris, 1896.	F. 63	Left	6 wks.	Cough.	Pain, dyspnea, tympany, coin sound, dislocation of viscera.	Rest.	Recovery.
40. Chauffard. Semaine Méd., 1896, vol. xvi. p. 156.	F. 20	Left	2 mos.	Exertion.	Pain, dyspnea, tympany, amphoric breathing; no sign of tuberculosis, no dislocation of heart.	Tested with tuberculin, no reaction.	Recovery.
41. Goodhart. Clinical Society Transactions, 1896, p. 29.	M. 24	Right and Left	Short time.	Jumping.	Pale, dyspnea, metallic tinkle, displaced heart.	Rest.	Recovery.
42. Aron. Deutsche med. Woch., 1896, p. 257.	M. 34	Right	6 wks.	.....	Cyanosis, hyperresonance, metallic tinkle, no respiratory sound, positive pressure in chest.	Tapped.	Recovery.
43. Gibson. Edinb. Hosp. Reports, 1896, vol. iv. p. 237.	M. adult	Right	.....	Exercising.	Partial coin sound, no breath sounds, no vocal resonance.	Rest.	Recovery.
44. West. Lancet, 1897.	M. 46	Left	.....	Unknown.	Pain, dyspnea, metallic tinkle.	Rest.	Recovery.
45. West. Ibid.	M. 24	Right	6 wks.	Cough.	Pain, dyspnea, bell sound, amphoric breathing, no tuberculosis.	Rest.	Recovery.
46. West. Ibid.	M. 24	Right	8 wks. 4 wks. 2 wks.	Foot-ball.	Three attacks; pain, dyspnea.	Rest.	Recovery.
47. West. Ibid.	M. 15	Right	2 mos.	Dancing.	Pain, usual sign.	Rest.	Recovery.
48. Osler. Maryland Med. Journ., 1897-98.	M. adult	Right	5 wks.	Walking.	Pain, dyspnea, cough, bell tympany, metallic tinkle.	Rest; tested with tuberculin, no reaction.	Recovery.
49. Atkinson. Ibid.	M. adult	.....	Few weeks.	Lifting.	Pain, faintness, amphoric breathing.	.....	Recovery.
50. Bushby. Liverpool Med. Chir. Journal, 1898, p. 97.	M. adult	Left	3 wks.	Cough.	Pain, heart not located, hyperresonance, no voice or breath sounds.	Rest and opium.	Recovery.
51. Finny. Dublin Journ. Med. Sci., Apr., 1898.	M. 18	Left	8 wks. and 5 wks.	Exertion.	Two attacks two mos. apart, pain, dyspnea, hyperresonance, metallic tinkle.	Rest.	Recovery.
52. Delafield. Interstate Med. Gaz., 1899, vol. vi. p. 14.	M. adult	Right	3 mos.	3 months, when dismissed	Sudden pain, amphoric breathing; dislocation of heart; author thinks it is tuberculous, but gives no reason.	None.	Under observation.
53. Whitney. Philadelphia Med. Journ., June 1, 1899.	F. 35	Left	9 yrs.	Brisk walk.	Dyspnea, cough, resonance, dislocation of heart, no fluid.	None.	Under observation.
54. Fussell. This paper.	F. 21	Left	2 wks.	During sleep.	Pain, dyspnea, dulness on percussion, absence of breath and voice sounds and of fremitus.	Tapped.	Recovery.
55. Rieman. This paper.	M. 27	Right	1 wk.	Cough.	Pain, no dyspnea, resonance, dislocation of viscera, no breath sounds.	Rest; strapping of chest.	Recovery.
56. Jochmans. Deutsch. Arch. f. klin. Med., 1902, Heft 1 and 2.	M. 22	Right	4 wks. 6 wks.	.....	Pain; patient always able to work. Tuberculin used with no effect.	X-ray showed collapsed lung.	Recovery.

Sex. The sex is mentioned in 55 cases. Of these 45 were in males and 10 in females. The large preponderance of males has long been recognized. West[13] published a series of 24 cases, and Hall[14] a series of 31 cases, including 21 cases of West's. In Hall's series there were only 2 females, about 1 per cent. In our series there were 2 per cent. of females. Hall believes, correctly, no doubt, that the preponderance of males is due to the fact that men are apt to make greater muscular efforts than women.

Age. There was 1 case under the age of ten years; between ten and twenty years there were 13 cases; between twenty and forty years there were 30 cases; over forty years there were 4 cases.

In 8 cases the exact age was not mentioned, but they were all young adults. The condition, therefore, is distinctly more frequent in young adults than in either the very young or the very old. No cases occurred between the ages of three and sixteen years.

Side Affected. This is mentioned in 50 cases. In 1 case the left side was the seat of the lesion in one attack, and the right side in the other. (Case 41, Goodhart.) Of the remaining 49 cases 24 were on the right side and 25 on the left side.

Duration. The actual pneumothorax may last but a few days, though its effects may persist from a few days to eight or ten weeks. One of our own cases was perfectly well at the end of two weeks; the second left the hospital at the end of a week, but was not entirely well then. When examined, about three months later, he was entirely well. Two cases remarkable for their duration have been reported; one is included in this series. The case reported by Whitney (Case 53, our series) appears to be a true case of spontaneous pneumothorax. It had lasted nine years, and was under observation at the time Whitney's article was written. Another case of protracted simple pneumothorax, the result of a pneumonia, is reported by Adams.[15] This case had occurred two years before it came under the care of Dr. Adams. There were typical signs of pneumothorax, with dyspnea on exertion. After the case had been under observation three years it gradually cleared up, and all the physical signs disappeared. Both of these cases, however, are marked exceptions. The duration averages, perhaps, six or eight weeks, although all the symptoms may disappear in a few days.

Exciting Causes. The exciting causes are not definitely known. The condition may supervene during sleep, as in one of our cases. Usually some violent exertion has preceded the attack—lifting weights, spasmodic cough, playing foot-ball, etc. It is probable that some such act is the usual exciting cause in most cases.

Symptoms. The symptoms are often slight. The patient of Jochmans (Case 56, our series) worked all the time he was under observation; but pain of marked severity, localized in the affected side, coming on suddenly and occasionally causing syncope, was present in practically all the cases. The pain, however, appears to last but a short time; at the end of twenty-four hours the patient was generally free from distress.

Dyspnea was absent altogether in the majority of cases. In one of our own it was marked, in the other it was absent. It is of a rather peculiar character—severe and constant in the beginning; later when the patient is lying still he is comparatively comfortable, but any exertion whatever causes him much distress.

Cyanosis was noticed in a few instances. It was present in the beginning of both our cases.

Unconsciousness occurred but once, and then apparently from the great pain and dyspnea.

Cough usually occurred, but was spasmodic in character and without accompanying expectoration.

Fever was not a marked symptom. In Case I. of our own observation there was a temperature of 102° F. in the beginning, but it lasted for only a few hours. In our second case fever was absent.

Physical Signs. Occasionally, as in the cases of Abeille (No. 10) and Johnson (No. 27) of this series, the physical signs were not marked when the patient was first seen, but they appeared gradually within twelve to twenty-four hours.

Mensuration is helpful in the diagnosis, as by that means a distinct enlargement of the affected side is usually shown. Thus in our second case the right side, which was the seat of the pneumothorax, was 1¼ inches larger at the level of the axillæ and of the nipple, and 1 inch larger at the level of the ensiform cartilage. In young individuals a compensatory emphysema on the healthy side may cause that side to be larger than the one affected with pneumothorax. The nipple is likely to be higher on the affected side than on the healthy one.

Inspection revealed enlargement of the affected side and bulging of interspaces in all but one or two of the cases in which it is mentioned. There was also loss of motion on the affected side. The apex-beat of the heart was dislocated to the right or to the left, according to the side affected. In a few instances—Heitler (No. 22), Chauffard (No. 40), and Galliard (No. 33)—the apex was seen in the normal position. In two cases (those of Lundie and Bushby, Nos. 36 and 50) it was not visible. In these cases there may have been pericardial adhesions, retaining the heart in the normal position; or the pneumothorax may have been

only partial. In our second case the veins over the affected side were enlarged.

Palpation revealed loss of tactile fremitus on the affected side in all but one case. This appears to be the most constant of all signs. The edge of the liver may also be felt low down in the abdomen, but occasionally the liver cannot be felt in the abdomen, despite the fact that the hepatic dulness is absent from its normal place.

The displacement of the heart is an interesting phenomenon. Most writers attribute it to the effect of pressure, the mediastinum being pushed to the opposite side by the air under pressure. No doubt this is a factor, but another of much importance is the elastic traction of the healthy lung. The heart, as Powell[16] has shown, is held in place by the balanced traction of the two lungs, which, to use Fowler and Goodlee's[17] simile, act upon it like two rubber bands pulling in opposite directions. When one of these bands is divided, as is the case when the lung becomes collapsed, the other band pulls the heart toward its own side. This theory explains the immediate displacement before the pneumothorax has attained a high degree.

Percussion. In all but three of our series of cases the percussion note is described as hyperresonant or tympanitic. In two there was a dull note on percussion. In Case I. of our own and in the case of Waller (No. 35, our series) there was distinct dulness over the affected side. So great was the dulness in our own case that the condition was at first taken for one of pleural effusion. The note changed within twenty-four hours, however, and at the time of tapping there was hyperresonance over the affected chest. The dulness on percussion, which may not be distinguishable from that caused by liquid, is due to the great tension under which the air is held. The note on the unaffected side is more resonant than normal. The heart dulness will be found in an abnormal position, the mediastinum being pushed or drawn toward the healthy side, as is well shown in Figs. 1 and 2. The employment of percussion to locate the heart is not mentioned except in our two cases and in that of Lundie. Care must be taken in locating the heart dulness to recognize the compensatory emphysema on the unaffected side. In many cases absence of liver dulness was noticed when the right lung was affected. As the air gradually disappears from the chest the percussion note becomes normal at the apex, but remains for a time hyperresonant at the base, the bottom of the chest recovering its natural character more slowly.

Auscultation. There may be entire absence of breath sounds and voice sounds, as is shown by one of our own cases. When this is com-

bined with a dulness on percussion there is great danger of mistaking the condition for one of pleural effusion.

Usually there is absence of vesicular murmur, which is replaced by amphoric breathing. The voice sounds are generally amphoric in character. The coin sound was present in many of the cases, but was absent in some. Considerable discussion has arisen as to whether the "coin sound" may occur in any other condition than pneumothorax. That it does is proven by a case reported by Osler, in which there was a marked coin sound over the apex of one lung, although at postmortem only a large cavity in the lung and not a pneumothorax was found.

Metallic Tinkling. A musical sound of high pitch, resembling drops falling into liquid confined in a cavity, is of frequent occurrence. As West pointed out in 1884, this phenomenon is not necessarily due to the presence of liquid, the explanation usually given for it, inasmuch as it is frequently present when liquid is absent; in such cases it is probably due to the escape of bubbles of air from the ruptured lung into the distended pleural cavity. In none of these latter cases was there a collection of fluid following the entrance of air, as proven both by physical signs and, in some cases, by exploration with an aspirator.

The opening into the pleural cavity is probably soon closed in many of the cases in such a way that very little air finds its way out after the first escape. This is probable, as is shown by the rapid disappearance of air in most of the cases; and in the patients who had been tapped there was no return of air into the cavity, as there assuredly would have been if the opening had continued patulous. It is, therefore, seen that amphoric breathing and amphoric voice sounds are not necessarily, as has been held, signs of a patulous opening, but may occur when the opening is closed or valvular. That the opening is occasionally valvular, allowing the air to enter but not to leave the pleural cavity, is shown by the decidedly positive pressure of the air in the pleural cavity in some cases, as in the experiments of Aron,[18] made on a case of spontaneous pneumothorax. Hamilton has recognized this fact in his article.

Recurrence of Symptoms. This took place in six of the tabulated cases. In all but one of the instances the recurrence was on the same side as the original trouble. In one (that of Goodhart, No. 41) the recurrence was on the opposite side. In one case there were three recurrences (the case of Gabb, No. 34, in which there were four attacks, with intervals of six, two, and six years). In one instance (that of Finny, No. 51) the recurrence took place eight weeks after the first attack, when the patient seemed entirely well. In Flint's case (No. 26) there was an interval of four weeks.

A pneumothorax which is simple—that is, not accompanied with the formation of liquid in the chest—occasionally occurs in tuberculosis, and the patient may remain in good health for a long time.

West reports such a case. A man, aged twenty-four years, under treatment for tuberculosis of the lungs, was suddenly seized with severe pain in the chest accompanied by dyspnea and with the typical physical signs of pneumothorax. The patient recovered from this attack in six weeks without the formation of liquid in the chest.

Cayley[19] and Hale White[20] give examples of pneumothorax occurring in typhoid fever; others refer to the occurrence of the condition in lobar pneumonia. These cases have not been included in this series because they were due to some sort of inflammatory process in the lung. The cases which we have collected had no inflammatory condition.

One of us (Fussell) has observed a remarkable case of pneumothorax which occurred as the initial symptom of a case of primary sarcoma of the pleura. Though the case is not one which belongs under the heading of this paper, it was thought to be such a case for over three months. It is such a marked example of the difficulty of making a diagnosis that we report it somewhat at length. It is not included in the list.

CASE III.—John A., aged three years, and only child of healthy parents. No hereditary disease in either branch of the family. I have been his medical attendant since birth. He has never been seriously ill.

Suddenly in the night of December 14, 1901, he awoke from a sound sleep, crying with pain. During the next day he had a slight cough. I first saw him on the evening of the 15th. I made a cursory examination, but observed nothing especially wrong. At my visit on the 16th I observed that there was much dyspnea. When not disturbed the child was comfortable, but breathed rapidly. On examination the heart was found in the normal position. There was hyperresonance all over the right side of the chest. There was exquisite amphoric breathing and metallic tinkling. There was no succussion splash. Pectoriloquy could be heard over the entire right chest. The right side was motionless during respiration. There was no fever.

December 18th. Physical examination revealed the heart to be 3 cm. to the left of the nipple line. There was no fever. The liver dulness had disappeared.

21st. The amphoric breathing had disappeared from the apex of the chest, although it could be heard at the base. There was still hyperresonance.

22*d*. Vesicular breathing was heard at the apex of the right lung, to the third rib anteriorly, and to the angle of the rib posteriorly. The amphoric breathing was heard only at the base posteriorly. The heart's action was fairly slow.

26*th*. The heart was almost in its normal position. Breath sounds fairly well heard over the right chest.

February 1*st*, 1902. Patient moving about the house. The temperature had never been above normal. The liver dulness had returned. Breath sounds could be heard over the entire right lung, but they were not as good as over the left lung. The apex-beat of the heart was exactly under the nipple. There was no dulness.

6*th*. During the night following a day of too severe exertion, extreme dyspnea returned. On examination there was marked hyperresonance over the right chest. The heart-beat was in the anterior axillary line. Amphoric breathing, pectoriloquy, and metallic tinkling, with a typical coin sound, had reappeared. The liver could be felt on a line with the umbilicus. The patient was rather cyanosed, and the heart's action was rapid. The temperature was 102° F.—the first fever during the illness. There was evidently a reopening of the old rupture of the lung, or a rupture in a new place. The patient's condition gradually grew worse, and on February 11th he was almost *in extremis*. The chest was aspirated under local anesthesia. Much air, with a small quantity of bloody froth, escaped. Immediately the heart returned to its normal position, dyspnea disappeared, and good breath sounds were heard over the right chest. The child fell into a quiet sleep, and when he awoke asked for nourishment.

13*th*. The patient still pale, but not cyanosed. Good resonance over the right side to the liver dulness, which was in the normal position. Heart dulness was of normal size and in the normal position. Breathing was slow, regular, and full.

24*th*. There was good respiratory movement on both sides of the chest. Breath sounds not quite so loud on the right side as on the left. Heart and liver in normal position.

March 3*d*. The child appeared well. The breath sounds were still not quite so loud over the right chest as over the left.

Patient was sent to Florida March 1st. Was improving steadily until April 8, when suddenly, in the middle of the night, he was seized with pain and seemed to be trembling and cold. There was some shortness of breath. From that time on he became gradually more dyspneic; breathing rate about 60. Various diagnoses were made until Charleston was reached, and liquid was diagnosed in the chest.

April 16. *Physical Examination.* The patient lies quietly on the right side; but when disturbed he cries. He is not cyanosed. Crying does not cause cyanosis at first. After crying has continued and a little exertion is made, cyanosis is present. Bulging of the right side posteriorly. There is but little motion on that side. The apex-beat of the heart is not plainly seen, but it can be felt half an inch outside of the nipple line. Right chest measures 10½ inches; left, 12 inches. No fremitus on the right side. Large rhonchi are heard over the right side, possibly transmitted from the left. No coin sound; no metallic tinkling; no amphoric breathing. On quiet breathing, fairly good breath sounds are heard over the entire right side, but nothing to compare with those on the left. Percussion shows flatness over the entire right side posteriorly, resistance below the ribs on the right side, and good resonance over the right and left flank on lying down.

17*th.* The dulness still persists on the right side; no fremitus; distinct breath sounds on the right side; blowing breathing at extreme apex of the right side; left border of the heart dulness at the anterior axillary line. The patient was tapped in the mid-axillary line. There was practically no fluid present; only a small amount of blood and water that was in the tube at the time of operation. A hypodermic needle was entered in two other positions, but no liquid was found. After the operation the patient's left chest was almost tympanitic in character. Breath sounds were present. The patient could lie in comfort on the back—a thing not possible before.

18*th.* Patient breathing rapidly; lying on the right side; pale, but not cyanosed; abdomen distended. On the right side of the abdomen there is very much more resistance than on the left. The interspaces on the right side are still bulged. There is epigastric retraction; the exterior jugular vein is filled. There is tympanic resonance over the right side anterior to the margin of the ribs, and there is dulness posteriorly of the right side below the fourth rib. No tinkling, no amphoric breath sounds. The exterior jugular fills on crying. The heart dulness is almost in the anterior axillary line.

21*st.* Breathing is more labored than yesterday; there is resonance over the right chest as far as the sixth rib anteriorly and posteriorly. Dulness below that position. The dulness is not movable. The left border of the heart is one inch to the left of the nipple.

22*d.* The patient passed a restless night, is cyanosed, the heart action rapid and weak. Physical signs about as yesterday except the position of the liver, which seems to be on a decidedly lower line that it was yesterday. In the afternoon the patient was suffering so extremely,

and apparently was in such imminent danger of death, that ether was administered, a portion of the sixth rib excised, and the following conditions found:

There was a cavity lined with pleura which extended above the point of opening as far as the finger could reach. It contained 60 c.c. of bloody liquid. The whole lower chest was filled with a semisolid substance.

The patient bore the operation badly, but revived under stimulation, and was in good condition two hours after the resection.

24th. A sudden cardiac dilatation after a good night's rest.

26th. Death occurred. At the autopsy the right chest was found filled with a primary new-growth of the pleura. Rupture of the lung had occurred as the first sign of the disease.

A study of our own cases and of those we have collected from the literature shows that pneumothorax occasionally occurs in persons in apparent good health. This has been observed, as the cases we have collected testify; but the tendency of writers has been to ascribe such cases to an unsuspected tuberculous lesion that had remained and continued to remain unrecognized by physical and rational signs. We desire to emphasize the fact, however, that there is a spontaneous pneumothorax which is not due to tuberculosis of the lungs. What is its cause? The most reasonable view, it seems to us, is that the rupture of the lung occurs through an emphysematous vesicle. This presupposes the existence of an emphysema; hence, it might be said, a disease of the lungs. As we have tried to exclude from our tabulation all cases of pneumothorax occurring in advanced chronic emphysema, our list comprises only cases in which emphysema if it existed was moderate and not possible of diagnosis. Now a moderate degree of emphysema in adults cannot be considered a sign of disease. It is extremely rare to find an adult lung in which there are not a few enlarged vesicles along the anterior margins or at the apices. As this condition is not recognizable clinically, and as it is not considered a sign of disease postmortem, it is not necessary to do so when explaining spontaneous pneumothorax. Our conclusion, therefore, is that pneumothorax can occur, with a practically healthy lung, from rupture of an emphysematous vesicle.

The possibility of its occurrence as the result of emphysema is undoubted. A number of cases of pneumothorax are on record in which the autopsy showed advanced emphysema and no tuberculosis.

In Ranking's case, quoted in our series (No. 9), there was a spontaneous pneumothorax, with recovery. Some time after the patient died of an

unsuspected dissecting aneurism. At the postmortem a small superficial area of the lung that had been affected with pneumothorax was found to be the seat of emphysema. Ranking believed that the pneumothorax occurred because of the rupture of one of these vesicles. There was no tuberculosis. Devillier (the first case of our table) was unable to find at the postmortem any signs of tuberculosis, and believed the pneumothorax was due to rupture of an emphysematous vesicle which was found.

Cnopf[21] has observed several cases of diphtheritic croup which developed pneumothorax before death; at autopsy an emphysema, local in character, was found, rupture having taken place through one of the vesicles.

Zahn[22] reports six cases of pneumothorax caused by exertion in individuals suffering from some grave pulmonary lesion. He found either a rupture through a local emphysema or to a tear of the pleura due to old pleuritic adhesions.

That pneumothorax may occur with a practically healthy lung is clearly demonstrated by the cases in our table; the histories show that the individuals were perfectly well before the occurrence of the pneumothorax. The after-history is likewise one of perfect health. No severe inflammatory reaction followed the entrance of the air into the pleural cavity. In tuberculous cases the simple pneumothorax is soon followed by the formation of liquid in the chest. Tuberculous cases die in the great majority of instances or become chronic invalids.

In three of the cases in our list (Osler, Chauffard, and Jochmans) tuberculin was used without any reaction following. This would go to show that in these cases at least there was no tuberculosis.

Diagnosis. With the symptoms as described above—sudden severe pain in the chest, dyspnea, faintness, cough, and the physical signs of hyperresonance, amphoric breath and voice sounds, metallic tinkling, coin sound, dislocation of the viscera—all suddenly appearing, there can be no possible difficulty in making a diagnosis of pneumothorax. All these signs, however, are rarely present at the same time in the same case. In the very rare cases in which there is dulness on percussion, together with loss of tactile fremitus and voice sounds, the pneumothorax may readily be mistaken for a pleural effusion, as was done in our first case. The sudden appearance of the symptoms and signs in the course of a few minutes or hours will usually serve to mark the case as one of pneumothorax. Puncture of the chest with a long hypodermic needle should always be resorted to when the question is in doubt.

In the cases in which there is hyperresonance with absence of breath sounds, together with loss of tactile fremitus and voice sounds, the thought of emphysema will arise. In emphysema, however, the physical

signs are generally bilateral; in pneumothorax one side alone is affected. In the very rare cases of unilateral emphysema there may be more difficulty in arriving at a conclusion. There will be displacement of the viscera in pneumothorax, none in emphysema; the presence of vesicular murmur in emphysema, none in pneumothorax.

There may be great difficulty in the diagnosis from diaphragmatic hernia. In this condition the abnormal percussion note, as a rule, does not extend over so great a surface as it does in pneumothorax; gurgling over the affected side will be present in hernia, absent in pneumothorax. Auscultatory percussion—percussion over the abdomen, auscultation over the chest—reveals distinct transmission of the percussion note; and when the patient swallows water there may be splashing and gurgling noises. If strangulation is present the symptoms of this condition will help in the diagnosis. Attention to the same physical signs will aid in the differentiation of pneumothorax from an abnormally high position of the diaphragm on one side, with the consequent apparent presence of the stomach and intestines in the chest cavity.

The non-tuberculous cases will have to be distinguished from the extremely rare tuberculous cases which recover without the development of effusion. The history of the case and the absence of tuberculosis in any portion of the body will help. The use of tuberculin will cause a reaction in the tuberculous cases, no reaction in the non-tuberculous. The great difficulty in distinguishing these benign cases from malignant disease of the pleura with pneumothorax is well illustrated by the case we have reported. The final outcome is the only distinguishing feature in such a unique case.

In certain rare instances of extremely large tuberculous cavities all the signs of pneumothorax may be present, except dislocation of the viscera, which will serve to point the way to a correct diagnosis.

Case 56, by Jochmans, is of especial interest, because the X-ray was used to confirm or make the diagnosis. The collapsed lung could be seen as a shadow above a clear zone below. As the lung expanded its shadow was seen further down.

Treatment. The great majority of patients were put to bed and received an opiate to control the pain. No other treatment was necessary, as they soon began to improve. In our second case (No. 55 of table) strapping of the chest with adhesive strips proved effective in controlling the pain. Nine of the cases were aspirated, with instant relief of all symptoms and without return of air into the chest cavity.

Aspiration is certainly a safe procedure; it is entirely under the control of the operator, so that it can be stopped if untoward symptoms

occur. If the symptoms are urgent the case should be aspirated, and aspiration should also be performed if the air is not spontaneously absorbed in a few days.

It is wise, however, to delay aspiration for a few days after the rupture, in order that the seat of the opening may be firmly closed with lymph, otherwise the opening will rupture and the air re-accumulate.

Result. All but one case recovered (Case 1, 1826), but the true nature of this case was not realized until autopsy.

CONCLUSIONS. 1. Spontaneous non-tuberculous pneumothorax occurs in healthy individuals. It is rare. It is most common in young men.

2. The pneumothorax is simple—*i. e.*, there is no formation of fluid.

3. There is rarely any febrile reaction, except, perhaps, in the very beginning.

4. There is probably a moderate amount of emphysema in the lung which is not recognized during life and is not incompatible with health.

5. Aspiration is a certain and safe means of relief and should be resorted to in severe or prolonged attacks.

6. This form of pneumothorax is benign. All but one of the reported cases recovered, and there was only once formation of fluid.

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DISCUSSION.

DR. KINNICUTT: I have seen an instance in the last few years of a similar character in a young man who had never had a day's illness until taken with a sudden pain and came in suffering with an extreme degree of pneumothorax. He was immediately aspirated, made a good recovery, and at the end of four weeks was discharged apparently well. A considerable period afterward he was carefully examined again, and his chest showed no evidence of any lesion of any kind. I confess that I had always believed that in such cases there was a localized lesion of the lung, possibly of tuberculous nature, but no evidence of it could be obtained in this case.

DR. COHEN: In regard to the case reported from my service at the Philadelphia Hospital, I am not yet sure that there was no tuberculous element. It could not be found; that is all we can say. I think we are justified in suspecting tuberculosis unless there is evidence of an adequate mechanical cause. I have had the experience of mistaking for pneumothorax an enormous cavity; and I may add that the excavation being covered by scarcely more than thickened pleura, was practically a condition of pneumothorax. I do not think, however, that I should make the mistake again, because I should be on the lookout for it. Wherever the physical conditions are such as to give a resonating chamber in connection with a consolidated or compressed lung there will be found the metallic acoustic phenomena dependent on such conditions.

DR. F. C. SHATTUCK: It does not seem to me that recovery, however complete and permanent, or the absence of any local signs of tuberculosis, is sufficient in this connection absolutely to exclude tuberculosis; and I cannot but share the feeling expressed by Drs. Kinnicutt and Cohen that in many of these cases there is really a tuberculous background. In illustration of the latency of tuberculosis I will mention a little colored boy admitted to the Massachusetts General Hospital, under the care of Dr. C. A. Porter, for pistol-shot wound of the abdomen. Laparotomy revealed markedly enlarged mesenteric glands, presumably tuberculous. He recovered from the operation, and went out all right.

I have seen two of these cases of pneumothorax. On a visit to one of my patients she remarked that one of her servants was troubled with shortness of breath, and on examination I found the chest full of air. I tapped her two or three times, and she recovered. I also saw a man sent down from the country with the diagnosis of aneurysm, but he had a pure pneumothorax, probably the result of violent cough, and had to be tapped a number of times, but finally recovered, and is now perfectly well. It seems to me that if there is any one thing we have learned in late years it is the latency of tuberculosis and its innocuousness in many instances.

DR. JANEWAY: I have seen several cases of this nature, but must admit that it is a difficult problem to say what the etiologic factor is. It has seemed to me that in some a local empyema around a small focus of disease in the lung as a tuberculous focus, or such emphysema as occurs where there is a local pleuritic adhesion, may be accountable for the pneumothorax, especially where it occurs after forced exertion or violent cough. One of the cases I have met with was a young man who had run up five flights of stairs in a great hurry, and had been seized with violent pain in his left side. This, together with the consequent heart weakness, had led to a diagnosis of angina pectoris. He had simple pneumothorax, and recovered without aspiration, as have the other cases under my observation. As no infection of the pleura occurs from such perforation, no pleurisy develops and the air is absorbed. The difficulty of making out a small focus of tuberculous trouble is undoubtedly familiar to all. A spot no larger than a pinhead or a pea could not be ascertained. We all know how difficult or impossible it may be to detect the focus from which an hemoptysis has occurred a little time before, so that after a week or so nothing may indicate whence it came.

DR. PEABODY: An interesting case of this character appeared in the children's clinic in Vienna when I was a student there. A child had swallowed a dose of caustic potash and acquired an esophageal stricture. She was having it dilated by a bougie, and was taught to use the instrument herself. On one occasion its passage excited more cough than usual, and one side of the chest filled with air. She recovered that time, but a second accident of the kind followed, and she suddenly died.

A few years ago in one of the hospitals in New York my attention was called to a woman whose left chest was filled with air. A most careful examination showed no lesion of the lung. She recovered after aspiration, and it was not until some weeks later that examination revealed a few râles at the apex. There was no question at all that the trouble was tuberculous in that case, and I cannot help feeling myself that tuberculosis is the likely cause in most cases, although physical signs may not be sufficiently pronounced to assure the diagnosis.

DR. OSLER: I think the doctor suggested the tuberculin test in these cases. A man came under my care who had been in robust health, and without any exertion had a sudden pain followed by pneumothorax. He was given tuberculin, but he did not react.

I would like to call attention to one point in the physical signs of the early stages. The side of the chest may be very full, and yet the percussion note is flat, not tympanitic. One may be deceived for a day or two.

DR. BILLINGS: During the past year I have seen a unique case, the patient, a doctor, who was examined, as doctor patients often are, by a good many physicians, with a resulting disagreement as to the diagnosis. The patient, while walking on the street and inspiring deeply, felt a sharp pain

in the region of the left nipple, which was accompanied by a sense of suffocation. The pain continued for a considerable time afterward, and on examination there were found all the physical evidences of a pneumothorax. When a needle was thrust into the side the gush of air was sufficient to extinguish a candle.

Some of our colleagues insisted that it was not a spontaneous pneumothorax, but a diaphragmatic hernia which gave all the physical evidences of a pneumothorax, and that the gush of air came from a gut in the thorax and not from the pleural cavity proper.

DR. FUSSELL: I cannot say that I expected such a consensus of opinion that all of these cases are tuberculous. It is certainly true that many of them are, but it is also true that there are cases of spontaneous pneumothorax. Two cases had come to autopsy in which no tuberculosis was found and only a few emphysematous blebs. Scarcely an autopsy is made in adults in which such emphysematous blebs are not found at the apex. We have carefully excluded all cases in which there is reasonable doubt as to the presence of tuberculosis.

In regard to Dr. Billings' point, we refer to that in the paper—that a diaphragmatic hernia has been mistaken for a pneumothorax.

EOSINOPHILIA IN A RECENT CASE OF TRICHINOSIS.

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THE first case of trichinosis in which eosinophilia was recorded was in Prof. Osler's wards at the Johns Hopkins Hospital, studied by Thomas R. Brown.[1] The blood was examined daily for over two months. The total leukocyte count rose from 17,000 at entrance to 35,700 forty-four days later; then it declined until on the sixty-eighth day (which was when the patient was discharged) it was 11,000. The diminution from 35,000 to 11,000 was a pretty rapid one, covering a period of ten days, and after that date the variance was not great. The eosinophiles were 37 per cent. at entrance. The highest percentage was 68.2. The case was lost sight of, and so has not been reported since the date of discharge. A second case of eosinophilia was studied by Brown in April and May, 1897; a third in December, 1897. It was under observation for eight days, and the last record of eosinophiles was 34.7 per cent., with a leukocyte count of 9000. The case was subsequently seen July 10, 1898, six months later, and the count registered was normal. In a fourth case, reported by Brown,[2] the eosinophilia varied from 48 per cent., on August 10th, to 24 per cent., on October 2d, and on November 20th, 7.5 per cent. In January, 1900, Blumer and Neumann[3] reported a family outbreak of trichinosis, nine cases, each of which showed a marked eosinophilia. Cabot reports four cases with eosinophilia, varying from 7 per cent. to 37 per cent. Atkinson[4] reports a case in which the eosinophiles ranged from 35 per cent. to 58.5 per cent. The leukocytes were at one time 28,000. Gwyn[5] reports a case with eosinophiles ranging from 33

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[4] Philadelphia Medical Journal, June 3, 1899.
[5] Centralblatt f. Bacteriologie, vol. xxvi. No. 2.

per cent. to 65.9 per cent. during a period of six weeks. The leukocytes were at one time 17,000. Stump[1] found 52 per cent. of eosinophiles in a case. (No trichinæ found in muscles.) W. W. Kerr[2] reports two cases, the first of which, on examination, showed 25,000 whites, with 42 per cent. eosinophiles, the number getting up in one examination as high as 68.7 per cent. In the second case the first record was of 18.1 per cent. eosinophiles, which three weeks later had risen to 86.6 per cent., with a white count of somewhere about 20,000. At the latest report of the second case there were 17,000 whites and 68.2 per cent. eosinophiles. Brooks[3] examined the blood in a case, and at the time of admission to the Bellevue Hospital, February 2, 1900, 18,000 leukocytes, with 10 per cent. eosinophiles, were recorded; on February 12th, 44 per cent. eosinophiles; from then a steady increase up to 83 per cent., followed by a decline which on March 14th was 15 per cent. of eosinophiles. F. P. Kinnicutt[4] reported a similar case. Gordinier[5] mentions two, one having 77 per cent. and the other 29.9 per cent. of eosinophiles. From these twenty-five cases it may be concluded, says Cabot,[6] that the constant presence of eosinophilia in trichinosis during the active stage of the disease may be safely inferred.

The following cases by Drake[7] and Da Costa throw some doubt on the constant presence of eosinophilia in trichinosis:

Dr. Arthur K. Drake, the Assistant Superintendent of the State Hospital at Tewksbury, Mass., has had an opportunity of studying four cases of trichinosis among human beings, and also of studying the disease in a herd of two hundred swine in which trichinosis was prevalent. He made numerous blood examinations of the trichinous swine and autopsies in a number of them. From his examinations of the blood he concluded that there was no increase in the percentage of eosinophiles in the trichinous swine. In the four cases of human trichinosis where the examination showed the presence of trichinæ in the muscles there was at no time any eosinophilia while the patients were under observation.

The first one was a case which ran its course in about six weeks,

[1] Philadelphia Medical Journal, January 17, 1899. [2] Ibid, August 25, 1900.
[3] Medical Record, May 19, 1900. [4] Practitioners' Society, February 2, 1900.
[5] Medical News, October 20, 1900. [6] Clinical Examination of the Blood, 1901, 4th ed.
[7] Paper read before the Boston Society of Medical Sciences recently. Published in Journal of Medical Research, June, 1902.

and was fatal. The second was observed over a period of six or eight weeks. The third was under observation four months. The fourth was under observation two months. At no time while these patients were under observation was there any eosinophilia. These cases represent apparently original outbreaks and recrudescences of the disease.

The conclusions which Drake arrives at by a careful study of his cases are as follows: Eosinophilia may not be present during the course of trichinosis as shown by his cases, and that of Da Costa,[1] a traumatic recrudescence of trichinosis; and that although present in twenty-five cases reported in this country at the initial outbreak of the disease, it may not be present during the course and recrudescence of the disease, even if the infection be a severe one. Lastly, eosinophilia, with certain other signs, points to the diagnosis of trichinosis. The absence of eosinophilia should by no means eliminate the possibility of trichinosis being present, and recalls the fact that no one sign is pathognomonic of the disease.

The case I have to present is as follows:

John D., stableman, aged twenty-three years, single, born in England, and living in Boston, entered the Massachusetts General Hospital on April 6, 1902, with the following history:

Family History. Mother, aged sixty-eight years, died of cancer; father, aged seventy-two years; eight brothers and sisters, all living and well. Habits: very rarely drinks; smokes ten cigarettes a day or pipe; drinks four cups of tea or coffee.

Personal History. In good health all his life; had mumps, measles, and whooping-cough in childhood; had gonorrhea four years ago; denies having had lues. Three years ago had pneumonia; was sick two months in St. Bartholomew's Hospital in London. Best weight, 136 pounds.

Present Illness. Nine days ago took a severe cold; very chilly all the time; felt mean, weak; little cough; slight pain in front of thorax and throbbing in forehead, with cough; slight expectoration. Worked until twenty-four hours ago, but getting worse all the time; in bed since. No dyspnea or pain with long breath: bowels not moved for forty-eight hours.

Physical Examination. Well developed and nourished. Skin and mucous membranes of fair color. Pupils equal, and react to light and accommodation. Few herpetic lesions on lips. Tongue moist, with white coat. Teeth neglected and covered with sordes. Throat negative. Few small glands in groins. Heart: impulse and dulness in fifth space of nipple line, 10½ cm. from mid-sternum. No enlargement to right; action regular, fair force. Soft

[1] American Journal of the Medical Sciences, 1901.

systolic bruit at apex, not transmitted; second pulmonic sound increased. Pulses: equal, synchronous, fair volume, low tension. Arteries not palpable. Lungs: nothing abnormal found. Abdomen: full, soft, tympanitic, not tender, no masses. Liver: fifth space to costal margin not felt. Spleen not enlarged. Abdominal, cremasteric, patellar, and plantar reflexes normal. Genitals normal. No edema. Temperature, 102.8° F.; pulse, 110; respiration, 30. Hemoglobin, 85 per cent.; whites, 11,800; Widal, negative; iodophilia, 0. Urine: high, acid, 1028, albumin, sugar, bile, diazo, 0; chlorids, normal; sediment, slight, no casts or blood, rare leukocyte and squamous cell. Had a fair night, sleeping most of the time.

April 7th. Much better; temperature down; given a hypnotic pill, No. 1.

8th. Improving; slept well; coughs very little; temperature lower; lungs clear. Whites, 12,900; differential count, 400 cells: polymorphonuclears, 63.1 per cent.; basophiles, large, 2.5 per cent., small, 7 per cent.; oxyphiles, 27.4 per cent. Given sulphonal and trional, āā gr. x. The marked eosinophilia led us to foretell muscular tenderness and to look for trichinæ later. Patient has not eaten pork or ham for many weeks, but every day has had sausages. No pains in legs and no tenderness.

9th. Lungs still negative. A few more herpetic lesions.

10th. Temperature irregular and at times very high. No definite symptoms except fever. Very slight cough. Heart and lungs negative. Very slight tenderness over calves of legs. Whites, 16,200; iodophilia, 0; differential count, 400 cells: polymorphonuclears, 59.9 per cent.; basophiles, small, 10.1 per cent., large, 2.6 per cent.; oxyphiles, 27.4 per cent.

11th. Uncomfortable night, restless and uneasy. Pains all over the body, especially in the legs and back. Slight cough, but no pain or sputum. No diarrhea. Temperature, 103° F. Whites, 14,000; differential count, 400 cells: polymorphonuclears, 57.7 per cent.; basophiles, large, 1.2 per cent., small, 6.4 per cent.; eosinophiles, 34.7 per cent. Blood normal, except for eosinophilia. Given morphin solution, dram i.

12th. Whites, 13,000; idophilia, 0; differential count, 400 cells: polymorphonuclears, 46.3 per cent.; basophiles, 5.7 per cent.; oxyphiles, 48 per cent. Given morphin solution, dram i.

13th. Whites, oxyphiles, 49.3 per cent. Marked symptoms in muscles; much pain in all muscles with any movement; muscles of calves, thighs, and forearms tender to pressure. Feels very sick; coughs much, but only little sputum; no headache. Lungs and heart negative; no abdominal symptoms; bowels regular. About one gram of muscle cut from gastrocnemius for diagnostic purposes. (Microscopic examination, by Dr. J. H. Wright, of the piece of muscle sent for examination shows the presence of undoubted trichinæ in small numbers.) Urine: high, acid, 1025, albumin, slightest possible trace; sugar, bile, diazo 0; sediment, no blood, no casts, a few squamous cells. Given morphin solution dram iss and repeat dram i.

14th. Blood: hemoglobin, 90 per cent.; whites, 18,800; reds, 5,630,000; differential count, 400 cells: polymorphonuclears, 42 per cent.; basophiles, small, 9.5 per cent., large, 2.5 per cent.; oxyphiles, 46 per cent.

15*th*. Much better; temperature, 100° F. No pains in muscles. Whites, 17,900; iodophilia, 0; differential count, 400 cells: polymorphonuclears, 37.2 per cent.; basophiles, small, 9.4 per cent., large, 1.5 per cent.; oxyphiles, 51.9 per cent.

16*th*. Much better; temperature normal; no muscle symptoms; little cough. Physical examination negative. Given house diet and sulphonal, gr. x. Whites, 13,200; differential count, 400 cells: polymorphonuclears, 34.3 per cent.; basophiles, small, 9.5 per cent., large, 0.7 per cent.; oxyphiles, 35.5 per cent.

17*th*. Whites, 17,400; differential count, 400 cells: polymorphonuclears, 32.1 per cent.; basophiles, small, 12 per cent., large, 1.6 per cent.; oxyphiles, 54.3 per cent. Given hypnotic pill, No. 2.

18*th*. Stitches taken from incised wound of leg; healed. Whites, 10,800; differential count, 400 cells: polymorphonuclears, 39 per cent.; basophiles, small, 9.6 per cent., large, 2.3 per cent.; oxyphiles, 49.1 per cent. Sulphonal and trional, āā gr. x.

19*th*. Whites, 9000; differential count, 400 cells: polymorphonuclears, 38 per cent.; basophiles, small, 10 per cent., large, 8 per cent.; oxyphiles, 44 per cent.

20*th*. Whites, 13,600; differential count, 400 cells: polymorphonuclears, 42 per cent.; basophiles, small, 9 per cent., large, 6 per cent.; oxyphiles, 43 per cent. Given hypnotic pill, No. 1.

21*st*. Whites, 10,700; differential count, 400 cells: polymorphonuclears, 44.8 per cent.; basophiles, small, 15.1 per cent., large, 5 per cent.; oxyphiles, 35.1 per cent. Given sulphonal and trional, āā gr. x.

22*d*. Whites, 12,600; differential count, 400 cells: polymorphonuclears, 64.6 per cent.; basophiles, small, 11.7 per cent., large, 3.5 per cent.; oxyphiles, 20.2 per cent. Given calomel, gr. $\frac{1}{10}$, every hour, ten doses, or free catharsis. Gaining rapidly; up and about the ward. No signs or symptoms.

23*d*. Whites, 11,700; differential count, 400 cells: polymorphonuclears, 50.4 per cent.; basophiles, small, 17.8 per cent., large, 7.5 per cent.; oxyphiles, 24.3 per cent.

24*th*. Temperature up to 100.5° F. No symptoms except slight coryza and some muscle pains. Whites, 14,800; differential count, 400 cells: polymorphonuclears, 69.8 per cent.; basophiles, small, 9.3 per cent., large, 1 per cent.; oxyphiles, 19.9 per cent. Given urethan, gr. xv.

25*th*. Temperature and pulse normal again this morning. Coryza better. Whites, 19,400; differential count, 400 cells: polymorphonuclears, 55.5 per cent.; basophiles, small, 9.8 per cent., large, 1.7 per cent.; oxyphiles, 33 per cent. Given urethan, gr. xv.

26*th*. Whites, 12,600; differential count, 400 cells: polymorphonuclears, 50 per cent.; basophiles, small, 13.5 per cent., large, 2.7 per cent.; oxyphiles, 33.8 per cent. Hospital cough mixture, dram i, every two hours, p. r. n. Urethan, ℥xv.

27*th*. Feeling well; up and about the ward; no symptoms. Physical examination negative. Whites, 11,000; differential count, 400 cells: poly-

morphonuclears, 55.5 per cent.; basophiles, small, 14.6 per cent., large, 3.1 per cent.; oxyphiles, 26.8 per cent.

28*th*. Whites, 14,300; differential count, 400 cells: polymorphonuclears, 68 4 per cent.; basophiles, small, 10.3 per cent., large, 1.6 per cent.; oxyphiles, 19.7 per cent.

29*th*. Whites, 20,600; differential count, 400 cells: polymorphonuclears, 67.1 per cent.; basophiles, small, 13.9 per cent., large, 8 per cent.; oxyphiles, 16 per cent.

30*th*. Whites, 11,500; differential count, 400 cells: polymorphonuclears, 66.3 per cent.; basophiles, small, 11.7 per cent., large, 1 per cent.; oxyphiles, 21 per cent.

May 1*st*. Whites, 17,600; hemoglobin, 95 per cent.; differential count, 400 cells: polymorphonuclears, 57.7 per cent.; basophiles, small, 10.9 per cent., large, 1.6 per cent.; oxyphiles, 29.8 per cent.

2*d*. Whites, 17,600; reds, 5,890,000; differential count, 400 cells: polymorphonuclears, 58 per cent.; basophiles, small, 16.5 per cent., large, 0.8 per cent.; oxyphiles, 24.7 per cent.

3*d*. Whites, 15,700; differential count, 400 cells: polymorphonuclears, 70 per cent.; basophiles, small, 10.7 per cent., large, 1.6 per cent.; oxyphiles, 17.7 per cent.

4*th*. Whites, 15,000; differential count, 400 cells: polymorphonuclears, 72 per cent.; basophiles, small, 9.5 per cent., large, 1 per cent.; oxyphiles, 17.5 per cent.

5*th*. Whites, 21,800; differential count, 400 cells: polymorphonuclears, 62 per cent.; basophiles, small, 14.5 per cent., large, 1 per cent.; oxyphiles, 22.5 per cent.

6*th*. Whites, 19,400; differential count, 400 cells: polymorphonuclears, 67 per cent.; basophiles, small, 9 per cent., large, 2 per cent.; oxyphiles, 22 per cent. Feeling perfectly well; out-of-doors nearly all the time.

7*th*. Whites, 21,800; differential count, 400 cells: polymorphonuclears, 65.8 per cent.; basophiles, small, 13.1 per cent., large, 2 per cent.; oxyphiles, 19.1 per cent.

8*th*. Whites, 16,300; differential count, 400 cells: polymorphonuclears, 50 per cent.; basophiles, small, 12.5 per cent., large, 3.1 per cent.; oxyphiles, 34.4 per cent.

9*th*. Whites, 14,100; differential count, 400 cells: polymorphonuclears, 54.7 per cent.; basophiles, small, 14.1 per cent., large, 1.8 per cent.; oxyphiles, 29.4 per cent.

10*th*. Whites, 16,000; differential count, 400 cells: polymorphonuclears, 50 3 per cent.; basophiles, small, 12.9 per cent., large, 1.6 per cent.; oxyphiles, 35.2 per cent.

11*th*. Whites, 24,700; differential count, 400 cells: polymorphonuclears, 50 per cent.; basophiles, small, 11 per cent., large, 1.75 per cent.; oxyphiles, 37.25 per cent. No physical signs; physical examination negative. Discharged well.

June 16*th*. Patient apparently perfectly well and at his work. Whites,

8000; differential count, 400 cells: polymorphonuclears, 38.5 per cent.; basophiles, small, 26 per cent., large, 4 per cent.; oxyphiles, 32 per cent.

The differential counts were made by Drs. E. A. Locke and R. Spaulding, while the literature was looked up by Dr. Frederick T. Lord, and I can vouch for their accuracy.

Trichinosis without Eosinophilia.

Howard. One case, Philadelphia Medical Journal, 1899, vol. iv. p. 1085. (Slides were examined and showed no eosinophilia, but no differential count was made.)

Da Costa. One case, American Journal of the Medical Sciences, 1901, cxxii. p. 725.

Drake. Four cases, Journal of Medical Research, June, 1902.

Trichinosis with Eosinophilia.

Thomas R. Brown. One case, Johns Hopkins Hospital Bulletin, April, 1897, pp. 79–81. Two cases, Journal of Experimental Medicine, 1898, vol. iii. No. 3, pp. 315–347. One case, Medical News, January 7, 1899.

Atkinson. One case, Philadelphia Medical Journal, June 3, 1899.

Gwyn. One case, Centralbl. f. Bakt. u. Parasit., 1899, vol. xxv. p. 746.

Blumer and Neumann. Nine cases, American Journal of the Medical Sciences, January, 1900.

F. P. Kinnicutt. One case, Practitioners' Society, February 2, 1900. Quoted from Cabot. (I cannot find this case.)

Harlow Brooks. One case, Medical Record, May 19, 1900.

W. W. Kerr. Two cases, Philadelphia Medical Journal, August 25, 1900.

H. C. Gordinier. Two cases, Medical News, 1900, vol. lxxvii.

H. F. Vickery. Two cases, Boston Medical and Surgical Journal, May 16, 1901.

G. G. Sears. One case, Boston Medical and Surgical Journal, May 30, 1901.

A. J. Patek. One case, American Medicine, June 15, 1901.

R. C. Cabot. Four cases, Clinical Examination of the Blood, 1901, fourth edition, revised.

Thomas McCrae. One case, American Journal of the Medical Sciences, July, 1902. (A case of typhoid fever, with trichinosis and eosinophilia.)

Stump. One case, Philadelphia Medical Journal, June 17, 1899. This case showed much eosinophilia in the blood, but no trichinæ were found in the muscles, which, however, presented a myositis. The case should, of course, not be classified with the above of trichinosis with eosinophilia.

TWO CASES OF SUPPOSED GASTRIC PERFORATION IN WHICH NO EXPLANATION OF THE SYMPTOMS WAS FOUND AT OPERATION.

By ANDREW H. SMITH, M.D.,
OF NEW YORK.

Case I.—F. B., aged twenty-eight years, waitress, admitted to Presbyterian Hospital March 8th. Pronounced tea-habit. No previous history of gastric disturbance except that ten days before admission she had had a dull, aching pain in the epigastrium after eating, but without nausea or vomiting. It was accompanied by flatulency and eructations of gas. Three days before admission she had an attack of faintness and cardiac palpitations, with a feeling of suffocation. An hour later she vomited a large amount of clotted blood. This was twice repeated within an hour. No melena. The day after admission she passed bright blood and mucus from the bowels. Movements frequent and painful.

Physical examination negative, abdomen soft; no tenderness, except in right iliac fossa, which was a little sensitive to pressure; temperature, 100.5° F.; pulse, 80; respiration, 20; red blood cells, 4,720,000; hemoglobin, 75 per cent.

The patient was at once placed on rectal feeding, which was continued until she was transferred to the surgical side, nothing being given by the mouth. Enemata well retained.

March 9th. Patient vomited several times bile and a little mucus.

10*th.* A small area of local tenderness was found in the epigastric region. At 1 P.M. she complained of epigastric pain, and the area found in the morning was much more sensitive and had increased in size. Temperature at 4 P.M. rose to 102° F., pulse to 120. The patient appeared more ill. Abdomen not distended.

11*th.* Pain still continues and has been more severe, though there has been no further vomiting. Abdomen still soft; local tenderness more pronounced, slightest touch causes extreme pain. Temperature, 101° F.; heart action and pulse weaker; pulse, 128; 8 P.M., pulse has risen to 140; weak and thready; heart sounds feeble; patient is in shock; looks very ill. Diagnosis, perforation or hemorrhage. Patient transferred to the surgical side. Operation at 11 P. M. Median laparotomy revealed normal peritoneal cavity.

The exterior of the stomach appearing normal, the viscus was not opened. Death occurred in twenty-four hours. Autopsy not allowed.

This case presented all the appearances of gastric ulcer, which is so common in young women, and particularly in those of the servant class. The supervention of epigastric pain and tenderness on the second day after admission, and the marked increase of these symptoms, together with the great acceleration of pulse on the third day, and a condition of shock, pointed to the occurrence of a very grave lesion. This was at once suspected to be perforation. The absence of symptoms of peritoneal infection was noted, but as the stomach was and had been for some time entirely empty, less weight was given to this absence than perhaps should have been allowed.

The urgency of the case seemed to call for an exploratory laparotomy, but the result of this did not warrant the additional shock of opening the stomach. The refusal of the friends to permit an autopsy left us in doubt as to the cause of the symptoms.

That they were not due, however, to hemorrhage *per se* is evident from the absence of blood from the last material vomited and from the stomach at operation.

CASE II.—J. M., female, aged twenty-seven years, admitted February 6, 1902. Habits good; no admitted tea-habit. There is an antecedent history of indigestion and gastric disturbance, with slight nausea and a little vomiting.

A week before admission gastric disturbance, beginning an hour after meals; no pain, but a sense of soreness. A little dark blood was passed from the bowels the following day.

Physical examination negative except for a slight murmur at the base and also at the apex. Temperature, 100.2° F.; pulse, 80; respiration, 20; no epigastric pain or tenderness. Rectal feeding at once begun; nothing given by the mouth.

February 7th. Patient vomited about six ounces of blood. This was repeated several hours later, only to a small amount. Movements black and tarry. Red cells, 6,000,000; hemoglobin, 90 per cent.; leukocytes, 15,000; urine, 1038; contained a trace of albumin and many epithelial cells.

Enemata were continued for six days. Then, in absence of gastric pain and vomiting, feeding by mouth was gradually resumed, until on the 16th patient was taking eight ounces of peptonized milk and twelve ounces of egg albumin water (representing the whites of two eggs) per diem.

During this time the temperature had been a little above normal, ranging from 99.5° to 101° F., with a pulse-rate of 80 to 100. There had been no pain, nausea, or vomiting. Mental condition good.

On the morning of February 16th patient became a little irrational, vomited her food and a large amount of bile-stained fluid. Pulse, 100; heart sounds and pulse remained in good condition. Abdomen soft; no tenderness or pain. Patient a little drowsy and apathetic. Leukocytes, 21,000.

During the day the heart action became more frequent (120), and in the evening the temperature rose to 103° F. There was repeated vomiting. At midnight this feature became more marked and the vomitus had a distinctly fecal odor, but there was still no pain, tenderness, or distention of the abdomen.

February 17th, 3 A.M. Temperature remains high, vomiting continues of the same character, but not frequent. Physical signs as before. 8 A.M., pulse and heart action have become very weak and frequent. Pulse, 134; weak and thready, barely perceptible. Area of cardiac dulness is obscured by tympany. Respirations are shallow and diaphragmatic. Breathing is apparently unimpeded; abdomen soft, but there is a slight muscular resistance; no local pain or tenderness.

Lungs: Anteriorly below the level of the left fifth rib there is an area of tympany extending to costal margin. Breathing sounds of undiminished intensity are heard over this area and extending as low as the umbilicus.

Patient had all this time a distinctly septic look, and she was transferred to the surgical side with a diagnosis of perforating gastric ulcer.

On opening the abdomen no free fluid or adhesions were found. Stomach was distended with gas, and contained a little brownish fluid, possibly disintegrated blood.

The mucous membrane was greatly congested, and in the lesser curvature was found an ulcer of the size and shape of a melon seed, which, however, extended only through the epithelial layer and showed no signs of recent hemorrhage. The edges of the ulcer were soft and not elevated. The ulcer was excised and the stomach well sutured to the wall of the abdomen. Saline infusion was resorted to, but death occurred in twenty-four hours.

Autopsy showed fatty degeneration of the liver, otherwise no gross lesion of any organ other than the stomach. Microscopic examination of the mucous membrane of the stomach showed tubercles, and a few tubercle bacilli were found.

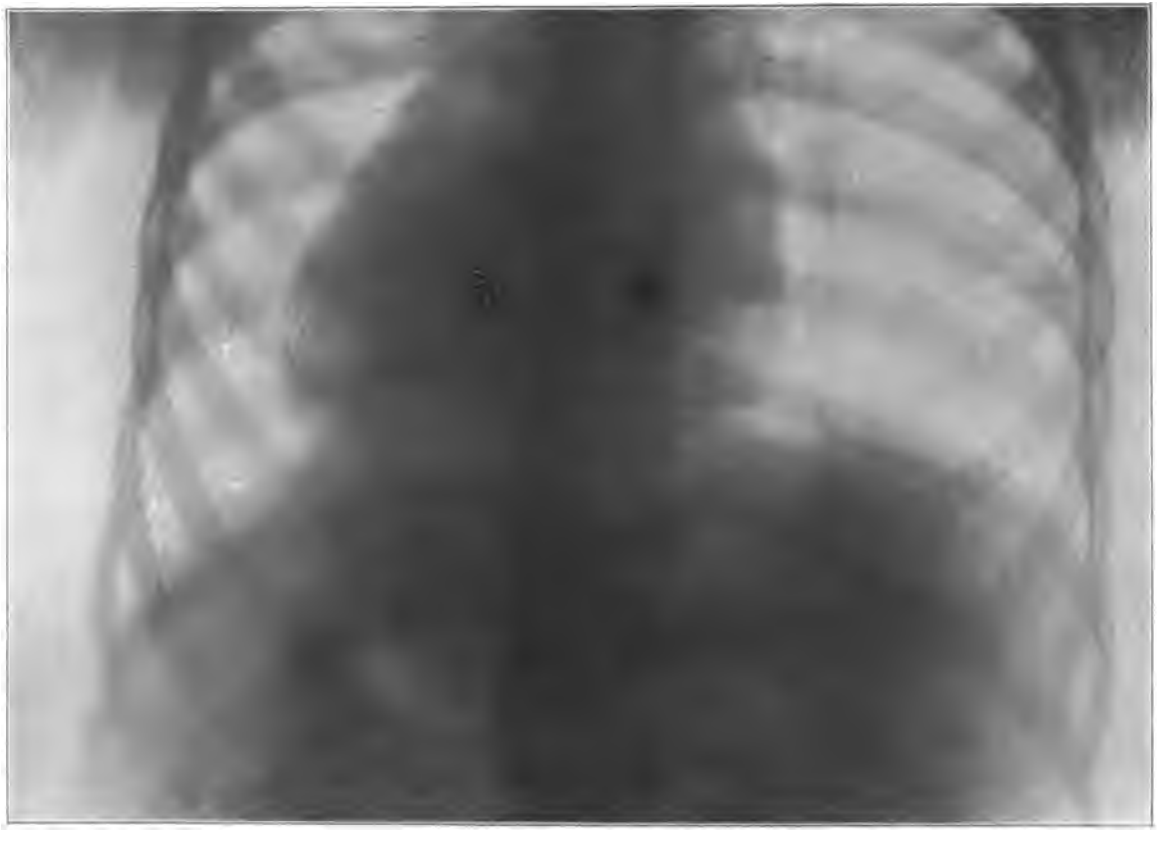
In this case the operation verified the diagnosis of ulcer, but did not explain the symptoms except in so far as the ulcer might have been a source of infection. The autopsy showed, in addition, tubercles in the gastric mucous membrane, but none elsewhere, and threw no further light upon the case.

A report of the microscopic examination of the stomach by Dr. George A. Tuttle is appended:

Microscopic Examination of Stomach. The superficial bloodvessels lying just beneath the surface of the mucous membrane are much dilated and filled with blood. Occasionally a vessel passing out between the tubules appears to be dilated, but generally the deeper lying portions of the bloodvessels appear normal. There are many small patches of lymphoid tissue lying on the mucosa, and some of them send prolongations between the tubules to the surface. Through most of the sections there are columns of small round cells between the tubules, which look like lymphoid cells. Two or three minute ulcers are found, the bases of which are covered with a thin

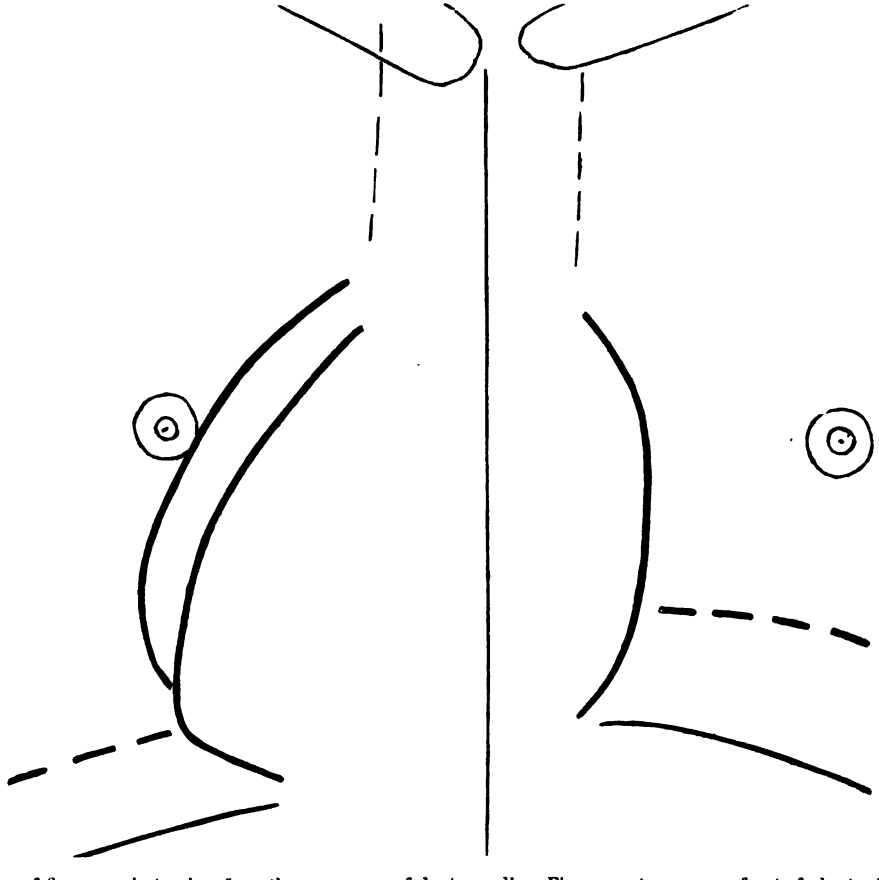
layer of leukocytes, and the underlying submucous tissue is more dense than normal and infiltrated with small round cells. The ulceration extends through the muscularis mucosæ, this layer ending abruptly at the edges of the ulcers. In almost all of the sections two or three minute tubercles of characteristic appearance are seen. These are round or oval patches of epithelioid cells, which stain more deeply with eosin than the surrounding cells, and from one to four or five typical giant cells are seen in most of them. There is a little small round-cell infiltration around them. More than one hundred sections were stained in the usual way for tubercle bacilli. Three or four rods of the proper size and appearance of tubercle bacilli were found and a few other similar rods of doubtful character.

FIG. 1.



Reproduction of radiograph from a case of dextrocardia. Radiograph taken with plate on front of chest. R indicates the right side of the chest. The dark circle over the spinal column indicates the point opposite which the anode of the vacuum tube was placed. The tube was twenty-six inches from the plate.

FIG. 2.



Reproduction of fluoroscopic tracing from the same case of dextrocardia. Fluorescent screen on front of chest. The two full lines near the right nipple indicate the position of the border of the left ventricle in expiration (outer line) and inspiration (inner line), respectively. The horizontal full lines indicate the position of the diaphragm in deep inspiration ; the broken lines, parallel with them, in expiration. The ends of the clavicles are indicated at the top of the cut.

A COMPARISON BETWEEN A RADIOGRAPHIC AND A FLUOROSCOPIC EXAMINATION IN A CASE OF DEXTROCARDIA.

By FRANCIS H. WILLIAMS, M.D.,
of Boston.

Both radiographic and fluoroscopic examinations of the chest are of value; the latter method is coming more and more into use, especially among French physicians. It requires a perfectly steady light, which is not necessary for taking radiographs, and as an apparatus giving such a light, namely, a large static machine, is not readily obtained, comparatively few physicians have had the opportunity of seeing what this method can accomplish. The present obstacles in the way of getting suitable apparatus will, however, probably soon be overcome.

A comparison between the two methods in a case of dextrocardia in a girl aged seven years, a patient of Dr. E. P. Joslin, at the Boston City Hospital, who was brought to me for X-ray examination, is of interest. The radiograph gave the position of the heart as indicated by the illustration (see Fig. 1), but the outline of this organ was seen with greater clearness by means of the fluoroscope (see Fig. 2); moreover, the characteristic pulsations of the left ventricle could be watched on the fluorescent screen, and the movement, during a deep inspiration, of the left side of the heart downward, and to the left instead of downward, and to the right, as in a normal individual, could be observed. That is to say, the fluoroscope not only gave the same information as the radiograph, but also added to it; further, the fluoroscopic examination was not subject to the delay incident to the photographic method. On the other hand, the radiograph has the advantage of being in itself a permanent record that can be filed with the case; but a permanent record of the fluoroscopic examination may also be made (see Fig. 2) and filed with the case by tracing on the skin the appearances seen, and then retracing them on tracing cloth.

A CASE OF ACUTE HEMORRHAGIC POLYMYOSITIS (POLYMYOSITIS HEMORRHAGICA, LORENZ).

By WILLIAM SYDNEY THAYER, M.D.,
OF BALTIMORE.

It is only within the last fifteen years that our attention has been called to the various forms of acute polymyositis apart from that occurring with trichinosis. Since the publications of Wagner,[1] Hepp,[2] and Jackson,[3] and Unverricht,[4] in 1887, a considerable number of observations have, however, been reported. Lorenz in his excellent study of diseases of the muscle, in *Nothnagel's Handbuch*, divides the polymyositides into the suppurative and non-suppurative forms. Acute non-suppurative polymyositis he distinguishes from instances of myositis in association with peripheral neuritis, such as have been reported by Senator,[5] Siemerling,[6] and others. The acute polymyositis Lorenz divides into (1) dermatomyositis; (2) polymyositis hemorrhagica; (3) polymyositis in association with erythema multiforme; (4) a number of unclassifiable cases. All these forms of acute polymyositis have, however, much in common, and it is a serious question whether one should regard such a classification as that of Lorenz as more than a mere division for clinical convenience.

The main symptoms of that type of polymyositis to which Unverricht has given the name dermatomyositis consist in the development, usually rather suddenly, though sometimes with prodromal symptoms of weakness and malaise, of local muscle stiffness, tenderness and pain, in association with extensive edema and cutaneous eruptions of varying character and extent. The edema in the

[1] Deutsche Arch. f. klin. Med., 1886-87, xl. 241.
[2] Berl. klin. Wochenschr., 1887, xxiv. 297.
[3] Boston Medical and Surgical Journal, 1887, cxvi. 498.
[4] Zeitschr. f. klin. Med., 1887, xii. 533.
[5] Deutsche Med. Wochenschr., 1893, xix. 933.
[6] Rev. de Méd., 1901, xxi. 426.

affected areas is often extreme, and commonly is of a hard, board-like character. The affected area may at first be slight, as in the case of Lépine, or it may involve the greater part of very large muscle groups. The muscles in the affected region are tense, swollen, and usually very tender. The tenderness may be extreme. The cutaneous eruption may be erythematous, papular, urticarial, and in some instances has shown the characteristics of erythema nodosum. Paresthesias in the affected extremities are not uncommon. These changes usually spread from one part to another, involving sometimes the majority of the voluntary muscles. Fever is almost always present, though it may be of moderate extent. Edema of the face and eyelids, as in trichinosis, is a frequent symptom. The spleen is palpable. In several cases there has been more or less subsequent muscular atrophy. The course of the disease is generally progressive, death occurring in the majority of instances from exhaustion or affection of the pharyngeal or laryngeal muscles. Recovery occurred in but five of twenty cases tabulated by Steiner.[1] In the acute stage the affected muscles showed marked edema, together with various degenerations, granular, waxy, fatty, and vacuolic changes. In the earlier stages there is more or less interstitial small-celled infiltration in the affected areas.

From this class of cases Lorenz distinguishes polymyositis hemorrhagica. Here the onset is apt to be somewhat more sudden and associated with less fever, though this is by no means always the case. In most instances the onset is associated with the development of a relatively small, nodular, tender area, generally in one of the muscles of the extremities; this is rapidly followed by more or less extensive edema, which may be as marked as in dermatomyositis. The skin may show a hemorrhagic or measly eruption, while later a yellowish-green discoloration may give evidence of the presence of deeper extravasation of blood. The course is much as in dermatomyositis, the percentage of recoveries among the reported cases being, however, somewhat higher—four out of nine cases which I have collected. The general symptoms are usually less severe than in dermatomyositis, and, as Lorenz says: "The muscle disease as

[1] Unpublished communication to appear in Journal of Experimental Medicine. Dr. Steiner has kindly allowed me to examine his manuscript. This article contains a valuable study of the literature and a full table of references.

such—that is, the inflammatory affection of each separately diseased muscle—represents a more or less independent process which runs its course independently of the inflammation in other muscles, and affects the general condition of the patient either because of the implication of vital muscles or as a result of the great number of muscles affected." Lorenz especially emphasizes the frequency of circulatory symptoms due to affection of the heart muscle. In some instances, as in the case of Fenoglio,[1] marked atrophy may follow the acute symptoms. The excised muscle has shown changes varying from simple hemorrhage, between unchanged muscle bundles as seen in the case of Neubauer, to appearances similar to those observed in cases of dermatomyositis, with the addition of a greater or less amount of interstitial hemorrhage. In later specimens more or less marked atrophic and sclerotic changes are found.

In addition to these types, Lorenz places in a separate class the myositis sometimes observed in association with erythema multiforme. The clinical symptoms are in most respects similar to those observed in the preceding classes, and the excised muscle in one instance showed like changes.

In another group Lorenz places a few typical cases which he has been unable to classify.

The etiology of polymyositis is as yet uncertain. Its association, in a number of instances, with tonsillitis or other infectious processes, together with the fever and severe constitutional symptoms sometimes observed, has suggested its possible infectious origin. The observation of Bauer,[2] Georgievkyi,[3] and Bacialli[4] would tend to support this theory. Others have believed the condition to be due to the absorption of poisonous substances from the gastrointestinal canal.

The following case, which would seem to fall into Lorenz's class of polymyositis hemorrhagica, is believed to be worth reporting on account of the rarity of the condition.

X., aged thirty-four years, married, a patient of Dr. Barshinger, of York, Pa., consulted me on February 21, 1902. His mother died of tuberculosis. In other respects his family history was good. He had had measles, mumps, and whooping-cough as a child. At one period as a young man

[1] Rivista Clinica-Arch. Ital. di Clinica Medica, 1890, xxix. 497.
[2] Deutsche Arch. f. klin. Med., 1899, lxvi. 95.
[3] Bolnitsch. Gaz. Botkina, 1901, xii. No. 16.
[4] Il Policlinico, 1902, No. 13, Seg. Med., fasc. 1 and 2, 16.

he was rather dissipated, but of late years he has been temperate. Urethritis fourteen years ago. For fifteen years he has had what he calls "rheumatism." In his own words: "As well as I can remember I was troubled with rheumatism about fifteen years ago, and off and on ever since that time. The worst attack did not stay with me more than a day or two at a time. It starts in the different joints and feels like an electric shock going through the joints and muscles of my arm and leg, jumping from the right arm to the left arm and from the right leg to the left leg, and my worst pains acting and feeling about like the worst shock you gave me yesterday. The pain shoots through the joints and muscles and makes them twitch and cause me a great deal of pain, but if I remain very quiet it generally passes off in a few minutes. At times I have to remain quiet or in bed the best part of a day before the pain will cease. Very often, when they attack me in the afternoon, by going right to bed it will pass off by the next morning. While these attacks were very seldom years ago, of late years dampness or cloudy weather brings them on."

On December 21, 1899, while doing some heavy lifting he "wrenched" his arm, and "it appeared as if the joint in the shoulder had jumped out of the socket." There was no great pain, but the whole arm became greatly swollen. This was especially marked in the upper arm. There was some slight dull pain in the shoulder. The forearm and hand showed a softened edema. The upper arm was hard and board-like, especially along the region of the biceps, and was of a purplish color, looking, as the patient expressed it, as "if a vein had burst." After three or four days everything cleared up. Six or eight months later the arm again became greatly swollen and purplish along its flexor side and somewhat so on the forearm. There was also slight pain in the front of the chest running back through the shoulder. This lasted for about ten days, after which he was quite well until one day last autumn when, after a fall, he felt a slight snap in the dorsum of his left foot. This was followed by edema of the foot and leg which lasted for several weeks. His physician states that the foot at this time was very red and somewhat mottled in appearance, but he is uncertain as to whether there was any distinct muscular hardness in the leg. The edema of the leg disappeared after several weeks, but the foot remained edematous for several months. Excepting for these attacks the patient has felt perfectly well, though whenever he lifts any heavy weight a slight transitory swelling commonly follows in his right arm and shoulder. "It seems that from that time (the initial attack) on, my arm was weak, and if I exercised it or lifted anything heavy with it I would get pain in the shoulder, and it would commence to swell up again." In a later letter he says: "There is seldom if ever a day goes by that I do not have a little shooting pain in some of my joints or muscles. My right arm for the last two years has felt more or less numb at times, and very often feels as if pricked with needles, and this has been getting worse; and at the present time this numbness or sleepiness very seldom, if ever, leaves my arm. My hand and fingers are seldom without the numb feeling, and nearly always

feel as if they were pricked with needles. This feeling may leave me on a very bright, clear day; but while to-day is a very bright and cheerful day, I have this numb feeling in my right arm, and my hand feels numb, as if it was pricked with needles, something like taking an electric shock all the time."

Six or seven days ago, at about three o'clock in the afternoon, without apparent cause, the right arm suddenly began to swell. This was associated with a slight tingling, stinging sensation. By the end of five hours the swelling of the upper arm was so great as to entirely fill out a loose shirt sleeve. The skin was red and hard, and board-like, though there was slight pitting on firm pressure. Three days after this the forearm and hand became edematous—a soft edema. There was no severe pain excepting for occasional slight stinging, lancinating sensations in the affected area, and a general feeling of numbness extending down into the hands—a sensation as if a bee were stinging him. Twenty hours ago when he went to bed there was marked edema of the right forearm and hand. On waking up in the morning he found that this had entirely cleared up. While the swelling had diminished to a certain extent in the upper arm, he noticed a fresh swelling of the right breast. There is a slight stinging pain at the present time in his right chest and arm. There has never been any very great tenderness in the affected area. He feels perfectly well in all other respects. The doctor thinks there has been no fever.

Physical Examination. The patient is a healthy looking man; the lips and mucous membrane are of good color; the tongue clean; the skin cool. Pupils, equal; respond well to light and accommodation; no nystagmus. On inspection the right arm and shoulder are considerably swollen, and also the right pectoral region as compared with the left. The swelling of the arm extends from the shoulder to the elbow, and is limited almost entirely to the bicipital region. The posterior part of the deltoid is also considerably swollen. There is distinct enlargement of the pectoralis major on the right, the external fold being clearly thickened. The biceps is apparently greatly enlarged, standing out as if in marked contraction. On the right, as the arm is hanging by the side it measures at its largest point 35.4 cm.; on the left, 29 cm. The skin over this area is tense and somewhat reddened. Above it is not edematous, below it is more reddened; and over about the lower third of the forearm, especially on the inner side, where it extends a little farther upward than it does in front, it is of a deeper, more cyanotic color, and very hard and board-like, pitting, however, on firm pressure. In a small area, about 6 or 8 cm. above the elbow, there is a transverse purplish discolored area about 4 x 1 cm. in extent. In the axilla and around below the pectoral fold there is a distinct yellowish-green discoloration of the skin, suggestive of deep hemorrhage. There is a slight enlargement of the right mamillary gland. The redness, the patient says, is much diminished. There is apparently no swelling whatever of the triceps. The infraspinatus and teres muscles are very prominent on both sides.

There is crepitus about the shoulder-joint as the patient moves the arm up and down, marked on the right, slight on the left. This appears to rise in the substance of the deltoid muscle. The power of the right biceps seems to be fairly good. On account of the condition of the muscle it was deemed inadvisable to allow the patient to make much effort. It is striking that although the swelling of the arm gives the impression of a contracted biceps, yet the movements of the muscles are scarcely to be felt when the patient flexes his forearm.

Heart. The apex impulse is visible and palpable in the fifth space 9½ cm. from the median line; the sounds are clear; the first slightly reduplicated at the apex. The second sounds are of normal relative intensity. The lungs are clear throughout. The abdomen is negative, excepting that the spleen is just palpable.

On the following morning the swelling of the arm appeared to be slightly diminished, though the discoloration in the axilla was a little more marked. A small piece of tissue, about 2 cm. in length by 2 to 3 cm. in depth, together with a little skin, was removed under cocain, by Dr. Tinker, from about the middle of the anterior surface of what was supposed to be the biceps. On cutting through the skin there was some edema, due in part, probably, to the cocain which was used; no apparent thickening; no evidence of inflammatory changes. There was very free bleeding from a small subcutaneous vein. On cutting into what was supposed to be the muscle there was a gush of about 150 c.c. of bloodstained serum. On squeezing the arm there presented at the opening a mass of old dark clot, probably dating from early in this attack. About 10 c.c. of this were squeezed out. The tissue removed was very pale and edematous in appearance, somewhat yellowish in color, with dark hemorrhagic streaks.

The *urine* was of rather pale color, acid; specific gravity, 1013; no albumin; sediment, inappreciable.

The *blood* showed: Red blood corpuscles, 4,328,000; colorless corpuscles, 4000 to the cm.

Dried specimens colored by Ehrlich's triple stain showed nothing remarkable in the appearance of the red blood corpuscles. A differential count of the leukocytes showed: Small mononuclear leukocytes, 23.1 per cent.; large mononuclear leukocytes, 9 1 per cent., and transitional forms; polymorphonuclear neutrophiles, 65.8 per cent.; eosinophiles, 1.7 per cent.; mastzellen, 0.8 per cent.

The patient left for home immediately after the removal of the tissue from his arm. Eight days later the arm had returned to its normal size and the stitches were removed, the wound having healed by first intention.

Sections of this tissue removed on February 22d were hardened in Zenker's fluid and stained by a variety of methods—hematoxylin and eosin, methylene blue and eosin, Van Gieson's stain, Mallory's stain, etc. Dr. MacCallum, who has kindly studied these specimens, makes the following report: "The specimen consists of skin with underlying subcutaneous tissue, and

supposedly part of the biceps muscle. Sections are made vertically through the skin in two directions at right angles to one another and stained by various methods. The skin with its appendages is normal. The small bloodvessels are surrounded by a loose net-work filled with cells of the type of plasma cells. Among the connective tissue vessels of the corium are many red blood corpuscles lying free. The subcutaneous tissue is extremely edematous, and there are considerable hemorrhages throughout it. In the wide spaces between the tissue elements there is a fine fibrillar net-work, possibly partly fibrin. In these meshes there are rather numerous round cells, somewhat larger than a polymorphonuclear leukocyte, with a single ovoid or slightly irregular nucleus and abundant protoplasm in which lie granules of a yellowish-brown color, probably iron-containing pigment produced by the destruction of blood in the adjacent hemorrhages. As the tissue was fixed in Zenker's fluid, tests such as Perl's ferrocyanid test are inapplicable. The subcutaneous fat lies in little masses through which abundant bloodvessels run. Some of these look as though new-formed. One of these is packed with leukocytes, and its walls are infiltrated with similar cells. Below these bundles of fat cells we reach a denser connective tissue in which the fibers are not so widely separated. There, as in the more superficial layer, are elongated cells with ovoid nucleus lying between the separated fiber bundles, which seem to be at least very young elements. These fibroblast-like elements seldom, if ever, contain the hematoidin pigment shown by the free round cells lying among them. Below this tissue lies a still more dense layer of connective tissue, made up of coarse bundles of wavy fibers, seen in Mallory's and Van Gieson's stains to be made up of connective tissue. In the interstices of this tissue the bloodvessels are extremely numerous.

Underlying this, which has the appearance of a fascial layer, there are only widely scattered bundles of mature connective-tissue fibers embedded in tissue made up almost entirely of one type of cell, but abundantly furnished with bloodvessels. This tissue varies in its density in alternating layers, through which the characteristic cells are the same, although the intercellular substance may be more or less compact. The cells have an elongated vesicular nucleus and a very long body which runs out at each end into a long delicate fibril. Often the cell body is branched, the process, like the cell body of the simpler forms, being drawn out to long sharp points. The quantity of intercellular substance varies, as stated, very markedly. It stains well with the connective-tissue stains. In the interstices there are great quantities of red corpuscles lying free. There is no muscle to be seen anywhere in the section. There is, therefore, beneath the fascia a great new-growth of tissue, the main mass consisting of cells of the type of embryonic connective-tissue cells, with numerous new-formed bloodvessels. Both in the connective-tissue cells and in the walls of the vessels mitotic figures are very abundant. This tissue, as well as the overlying tissue, is evidently edematous, and full of hemorrhage. No muscle is to be found.

These remarkable appearances, together with the clinical observation that the apparently greatly swollen biceps muscle could not be felt to contract when the arm was flexed, would appear to indicate that the muscle itself was buried in a mass of subfascial edema and hemorrhage, the clot being in the process of organization.

The patient was visited at his home on Sunday, April 26th. He states that although in good health he has been unable to lift heavy weights with his right arm, and is under the impression that when he attempts to do so a slight swelling of the biceps follows. He complains of weakness in that side, especially on lifting his arm to his head, and of numbness and tingling, especially in damp weather. The "shooting pains are increasing instead of diminishing."

On inspection, the patient looks well. The arms appear to be about equal in size, though the biceps is perhaps a little smaller on the right side than on the left. The forearms are equally well developed. There is still a slight discoloration at the point where the purpuric patch was previously observed. The extensor muscles stand out rather strikingly, more so apparently on the right than on the left. On the right side the arm measures 29.7 cm., the left 29. The right pectoralis major below and outside of the nipple appears to be slightly atrophied as compared to the left. The posterior part of the deltoid seems rather less prominent on the right than on the left, while there is a distinct flattening in the region of the infraspinatus. The same rather general plumpness of the muscles is observed as on the first examination. The grasp of the hand is good, slightly less powerful on the right than on the left. The power of the flexors of the forearm is also slightly diminished on the right. There is distinct loss of power in the right deltoid and pectorals.

Sensation to touch is everywhere good. Sensation to pain (prick of pin) is rather remarkably dull all over the body, but not more so on the right than on the left. The patient not infrequently fails to distinguish the head from the point of the pin, unless the stab be very sharp.

The deep reflexes at the elbow and wrist are with difficulty elicited on both sides.

There is no tenderness over the nerve trunks. After the tests of strength the patient complained of numbness and tingling in the right hand and fingers; the sensation, however, remained good.

Electrical examinaton shows a general diminished excitability to both galvanic and faradic currents in the biceps and flexors of the forearm on the right side, in the deltoid, and very strikingly in the right infraspinatus muscle, in which but little response could be obtained. The difference between the reactions on the right and left to both nerves and muscles appear to be quantitative rather than qualitative.

The essential features of this remarkable case appear to be recurrent attacks of swelling in various muscle groups. The more

severe attacks have been associated with evidences of deep hemorrhage (widespread discoloration of the skin), marked subcutaneous edema in the more affected areas, and, in one instance, a deep, almost erysipelatous reddening of the skin. Especially noteworthy is the fact that there have been very little pain and tenderness in the affected areas. Subsequently some of the affected muscles have shown undoubted areas of atrophy.

It is unfortunate that no muscle was obtained in the tissue removed from the arm. There can, however, be little doubt that the case belongs to Lorenz's class of polymyositis hemorrhagica.

The etiology of the case must be regarded as uncertain. The abruptness of onset of some of the attacks has been almost like that of an angioneurotic edema.

Further observations will doubtless throw more light upon the nature of the process. In the meantime the unusual character of the case would seem to justify the necessarily incomplete report.[1]

DISCUSSION.

DR. CABOT: I did not understand on what evidence Dr. Thayer based his diagnosis of myositis.

DR. JACOBI: If I understand the doctor correctly, I am of a rather different opinion in viewing these cases. The simplest form of myositis we know to be of traumatic origin; for instance, in those cases which occur in the newborn babe, where the finger or instrument of the obstetrician injures the sternoclavicular region, there you find a traumatic hematoma. The same thing is seen in boys injured when flying kites; here it also affects the sternocleidomastoid muscle, or in hard-working men, or in washerwomen who rupture their rectus abdominis muscle. *Multiple* myositides, however, such as described, are more frequently seen in cases of purpura, where you find a great deal of sensitiveness over the muscles, so that the patient cannot move for weeks or even months.

DR. THAYER: There would appear to me to be no serious question as to the classification of such a case as this. While the tissue removed from the right arm showed hemorrhage and edema existing, at that point at least,

[1] The patient was seen again in June during an attack in which there was remarkable swelling of the deltoid muscle and also swelling, edema, and discoloration of the skin over the ulnar group of muscles in the left forearm.

outside of the muscle substance proper, yet the history of the case and the condition of other muscles—the deltoid, infraspinatus and pectoral, for instance—were significant. The attack during which I saw the patient was almost like an angioneurotic edema, but the occurrence of repeated attacks of swelling limited distinctly to various muscles, associated with evidences of deep hemorrhage and followed by subsequent atrophy, would seem to me to justify placing the case in Lorenz's class of polymyositis hemorrhagica. Further observation of the case will probably settle this question.

A CASE OF PRIMARY DIPHTHERIA OF THE TRACHEA.

By ROBERT DAWSON RUDOLF, M.D.,
OF TORONTO.

Presented by A. McPHEDRAN, M.D.,
OF TORONTO.

Cases of primary diphtheritic involvement of the trachea are of such rare occurrence as to make any undoubted ones worthy of being recorded. Many authorities, indeed, altogether deny their occurrence, and believe that in those instances in which the condition has apparently occurred the primary seat of the disease has been higher up in the air passages, and has merely been overlooked. Thus, Dr. S. Gee, writing in Clifford Allbutt's *System of Medicine*, vol. i., page 749, says that "now and then a case is met with in which diphtheria is almost limited to the trachea. The tracheitis is not primary, but is preceded by a diphtheritic affection of the larnyx or fauces, which may have been slight or severe."

Most authors of standard text-books omit any mention of the condition at all, while others make a passing allusion to it, Fagge being an example of the former class, and Bristowe of the latter.[1] Northrop in the article on "Diphtheria" in Nothnagel's new *System of Medicine* has a short description of the condition, and states that it is most common after measles. He says that Goodall has reported several cases.

It is to A. Jacobi that we owe the greatest credit of minutely and accurately describing the condition, and one need make no apology for quoting his remarks on the subject in full.

In his *Treatise on Diphtheria*, 1881 edition, page 128, he writes as follows: "Primary diphtheria of the trachea does not occur frequently,

[1] Bristowe's Theory and Practice of Medicine, p. 212.

yet it can be diagnosed, and actual observation on the living and dead contradict flatly the opinion of many writers whose opportunities may have been limited. Quite recently (Klebs, *Handbuch d. pathol. Anatom.*, 1880, vol. vii., p. 283) Hans Eppinger risks the statement that 'croup and diphtheria occur also in the trachea, but only when descending from the larynx.' Without, occasionally with, an affection of the fauces; without general symptoms that would cause a feeling of anxiety to the parents; without more fever than anyone would expect in a slight bronchial catarrh; without much dyspnea, and after symptoms of a slight bronchial or tracheal catarrh which have lasted for a few days or hours, the little sufferers are most abruptly attacked by stenosis of the larynx. Within an hour, or even less time, they become cyanotic; tracheotomy affords but a temporary relief, or none at all; and the entire process occupies a very short space of time. Rarely is a large amount of membrane found in the larynx, but very much in the trachea and in the larger ramifications. The disease began there, and, without causing occlusion, because of the large size of the organ, ascended to the larynx, where it gave rise to a far more speedy death than is usually brought about by the descending croup. I have operated fifteen times in such cases; and no case, from the commencement of the urgent symptoms to death, ever lasted more than a day, but many a few hours only." He further states that death always occurs in these cases after operation, and that this is invariably caused by spreading downward of the membrane into the bronchial tubes, with consequent asphyxia.

Several years later, in Pepper's *System of Medicine*, vol. i., p. 671, he wrote thus: "It may happen that the trachea and bronchi may become affected, although diphtheria of the fauces does not exist. This does not occur as rarely as Henoch and Oertel seem to believe. They think that diphtheritic trachea-bronchitis is mistaken for the primary condition, because the throat is not examined early enough. Oertel is of the opinion that the membrane in the fauces is overlooked in such cases. Steiner (Ziemssen's *Handbuch*, vol. iv., p. 126), too, asserts that the tendency of the times is to question, nay, rather to deny, the existence of croup extending from below upward. Now, on the contrary, repeated experience enables me to assert with positiveness that diphtheritic trachea-bronchitis may occur without an affection of the pharynx at the same time. I do

not deny that it may last for days without giving rise to dangerous symptoms. I know it does. But when the process reaches the larynx the symptoms of suffocation become so urgent that tracheotomy may be absolutely required at once, and, in spite of the operation, death soon after occurs."

A somewhat extensive search through current literature for some years back yields only one record of a case of definite primary tracheal diphtheria. At the Harveian Society of London in 1899[1] Drs. Ewart and Hunt described "a case of diphtheritic membranous tracheitis, with temporary obstruction of the right bronchus in the adult, and exhibited a series of tube casts of the trachea expectorated on the third, fourth and fifth days of the attack. The patient, a woman, aged thirty-two years, was recovering, after a pyrexial period of nineteen days, from a severe pulmonary catarrh, shown by repeated cultivation to be diphtheritic. On the third day laryngoscopic examination showed the presence of membrane immediately above the glottis. The patient was aphonic for fifteen days, but the cough was not croupy, and there was no stridor or spasm of the glottis. She recovered." She was given a large quantity of antitoxin, and this, no doubt, was why she proved an exception to the statement made by Dr. Jacobi, in 1881, that all these cases are fatal.

The history of the case of primary diphtheritic involvement of the trachea, which I would record, is as follows:

A. B., a girl, aged four years, was admitted to the Victoria Hospital for Sick Children on October 31, 1901, under the care of Dr. Primrose, suffering from osteomyelitis of the tibia. Dr. Primrose operated for this condition on November 1st, and up to the 26th of that month she was considered to be progressing favorably. On the evening of November 26th her temperature was 99.8° F.—for her, not out of the ordinary. She appeared to have a slight bronchial catarrh. Next morning at 3.45 Dr. Chisholm, the house physician in charge, was called, and found the patient suffering from very urgent dyspnea, with great cyanosis. The nurse stated that it had only just come on. The condition was so violent that Dr. Chisholm tried to intubate, but no relief, in fact only aggravation of the symptoms, resulted. He then notified Dr. Primrose, who performed tracheotomy at 5 A.M. The patient was comatose at the time, and required almost no anesthetic. The operation at once relieved the dyspnea. At the time of the operation a culture was made, on blood serum, of the membranous material that came from the tracheal wound, and this in due time showed a pure growth of the Klebs-Loeffler bacillus.

[1] Lancet, February 11, 1899.

Dr. Wishart (the laryngologist of the hospital) and myself carefully examined the upper air passages and larynx some five hours after the operation, but could find absolutely nothing abnormal. The vocal cords were not even congested. Swabs taken from the fauces and nares gave negative results. The patient was beginning to breathe rather badly again, and was tranferred to the infectious wards under the writer's care.

Within the first forty-eight hours of her stay there she was given altogether 18,000 units of antitoxin, and for a time her general condition improved. Besides the free use of antitoxin, calomel inhalations were employed frequently, and various local applications were applied to the tracheal mucous membrane.

Quantities of diphtheritic false membrane came away from time to time through the tube.

The free inhalation of oxygen gave great relief for a time and seemed to prolong life for several hours, but the breathing became more and more obstructed, and the patient died asphyxiated on the third day from the onset of the acute symptoms. No postmortem examination was permitted.

Here, then, was evidently a case of primary tracheal diphtheria. How long the disease had been present before the urgent symptoms supervened it is impossible to say, but the patient was noted to have had a slight bronchial catarrh for several days. Jacobi points out that primary laryngeal and tracheal diphtheria are very frequently devoid of general symptoms, and believes that "this is due to the fact that the mucous membrane here is so freely supplied with mucous glands that the diphtheritic membrane becomes separated from the surface by a layer of mucus, and hence the lymph vessels of the mucous membrane are not influenced by the poisons to the same extent as elsewhere."[1] In the case of Drs. Ewart and Hunt, already quoted, the general symptoms were slight.

When in our case the urgent dyspnea set in, either the trachea immediately below the glottis had become suddenly plugged by the false membrane probably puckering up here and hence filling the lumen of that tube, or else a spasm of the glottis occurred from the entrance into it of a piece of the membrane, which acted as a foreign body.

Death was due, as already stated, not to toxemia, but to steadily progressing asphyxia from gradual spread of the process into the bronchial tubes.

[1] A Treatise on Diphtheria. A. Jacobi, 1881, p. 128.

OSTEITIS DEFORMANS AND HYPEROSTOSIS CRANII: A CONTRIBUTION TO THEIR PATHOLOGY, WITH A REPORT OF CASES.

By MORTON PRINCE, M.D.,
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THE symptomatology and general features of osteitis deformans have been so exhaustively discussed in this country within a recent period in the monographs of Elting, Wilson, and Packard, Steele and Kirkbride, that I shall limit myself in this communication to a brief description of a case and to the question of its pathology. The last-named writers have not only contributed a valuable addition to our knowledge of the anatomic lesions, but also an important summary of the data furnished by sixty-six cases collected from the literature.

CASE I.—Mrs. M., aged forty-four years, was referred on November 1, 1901, to my clinic at the Boston City Hospital from the Eye Department, to which she had applied for impairment of vision, but the ophthalmic records note only errors of refraction. She was referred to me for certain neuralgic pains in her head. The peculiar enlargement and deformity of the cranium and jaw were noticeable and led to a careful examination of the osseous system.

As to her previous history and the family history, they were practically negative. There were no evidences of syphilis. She had not had a pain or an ache referable to her present condition until April, 1901, when she had some dizziness (heart?), and a month later she experienced some pain in her head. From May to October she was free from pain and all other symptoms excepting the impaired eyesight, for which she was fitted with glasses. On November 1st her symptoms were mild, and, such as they were, consisted of neuralgic pains in the head, tinnitus aurium, and cardiac fluttering. Until two years ago she had never noticed any deformity of the bones—not until the curvature and enlargement of the right forearm were pointed out to her by a friend—and when first examined she was entirely unconscious of the extreme deformity of the skull that exists and of the obtrusive bending and thickening of the bones of the legs.

FIG. 1.

CASE I. Osteitis deformans, aged 44 years, showing deformity of jaw, right forearm, kyphosis and temporal artery.

FIG. 2.

CASE I. Osteitis deformans, showing enlargement of parieto-occipital region, arterio-clerosis, and deformity of radius, right arm.

On first inspection, aside from the asymmetry of the skull and jaw, the most noticeable peculiarity about her is the general degeneration of her physique. She looks much older than she is; she is short of stature, bent over, and has generally small, poorly developed muscles. There is a lack of color and vascularity of the skin, which has a dried and slightly yellow appearance. Physical degeneration is stamped upon her. She looks shrunken in height and development. On her temples enlarged and tortuous atheromatous arteries stand out and strike the eye. The heart is enlarged, the apex being one inch outside the mammillary line, but in the fifth space, and its action is heaving. A systolic murmur is heard over the aortic valves and at the apex, whither it is probably transmitted. The eyes are unusually prominent. (Figs. 1 and 2.)

Osseous System. The condition of the bones resembles in general that which has been frequently described in cases of osteitis deformans. The cranium is irregular and enlarged, although the hyperostosis is most obtrusive in the left parietal bone. The circumference of the fronto-occipital region is 61½ cm. The ramus of the jaw on the right is thickened and prominent to the eye; the spine is very slightly flexible, and has a marked kyphosis in the upper dorsal region. There is some deformity of the sternum from thickening; both clavicles are enlarged, the ribs thickened. The bones of the upper arms appear to be normal, but both radii, the right being the most affected, are thickened and curved, the bowing being outward. The last phalanges of the first and second fingers of both hands exhibit nodular thickenings and are distorted, being everted at an angle outward, giving the *impression of an osteoarthritis.*

Coming to the lower half of the body, both femora are curved and greatly thickened, as are the tibiæ. As in the forearm, the right side is more largely affected than the left; the bones of the pelvis are also involved in the process. The photographs and skiagraphs show fairly well the conditions present. Examination of the blood failed to throw any light on the morbid process, showing simply a mild secondary anemia.[1] (Figs 3 and 4.)

Examination of the nervous system at this time was negative.

Since my last examination of this patient she entered the Massachusetts General Hospital, where she came under the observation of Dr. Fitz, who also has made a careful study of her condition. While in this hospital she developed delusions and other mental symptoms, and was removed to the Boston Insane Hospital, where she is now under the charge of Dr. Lane, who has kindly furnished me with notes of her present condition, which is that of a rather mild stupor, with some depression and delusions.

The most interesting problems connected with this most interesting disease are its pathology and its relation to allied affections. The

[1] White count, 3800; red count, 3,768,000; hemoglobin, 65 per cent. Differential count: polymorphonuclear neutrophiles, 66 per cent.; small lymphocytes, 26 per cent.; large lymphocytes, 6 per cent.; eosinophiles, 2 per cent.

symptomatology has been adequately and exhaustively discussed within the limits of our present knowledge in the paper presented to this Association by Drs. Packard and Steele at the last meeting. It will be remembered that the basic and anatomic process in osteitis deformans as shown by the microscopic changes was summed up (but as I shall show incompletely) by these authors as follows:

"*a.* Absorption of the compact substance, causing enlargement and confluence of the Haversian canals.

"*b.* Formation of new bone, which runs diffusely through the affected and the adjacent healthy portions. This new bone remains uncalcified, and is in turn reabsorbed.

"*c.* The conversion of the medullary substance into a vascular connective tissue containing fat cells, giant cells, and leukocytes.

"*d.* As a consequence of these three processes the ordinary relations of the compact substance and medulla are destroyed. The bones become exceedingly thickened and asymmetrical, but since the new bone tissue remains uncalcified its elasticity permits of great deformity of the long bones from the weight of the body, and fractures do not occur."

This summary is incomplete in that it neglects to take into account the important fact that often *calcification does take place in the new bone*, and then a different picture is presented.

Clinically considered, the disease resembles in the peculiar enlargement and deformity of the skull what has been noted and described in hyperostosis cranii, or leontiasis ossa; and, although the two diseases are regarded as distinct, it is interesting to reconsider whether, after all, hyperostosis cranii may not be an incomplete development of the same process, and, therefore, the same disease. Putnam,[1] in his exhaustive and critical paper in 1896, has already recorded one case of my own of hyperostosis cranii. I have now to report another interesting case, which in general appearance and certain other respects bears a most striking resemblance to the case of osteitis deformans I have just reported.

CASE II.—The patient, Miss A., is sixty-three years of age, and looks about ten years older. Her general physical appearance is that of degeneration. She is short and considerably shrunken from her former height, due to the marked kyphosis in the cervicodorsal region. The anterior borders

[1] American Journal of the Medical Sciences, 1896.

Fig. 3.

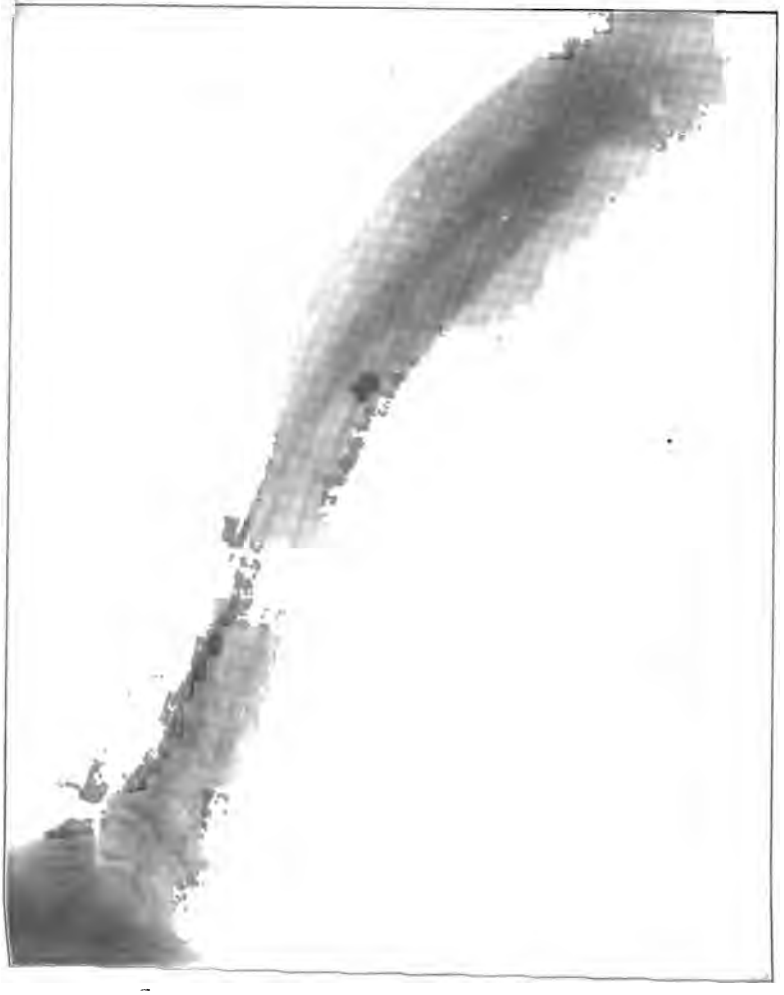


Fig. 4.

of the ribs correspondingly approximate the pelvis. There is very marked arteriosclerosis, which is particularly obtrusive in the temporal arteries, which stand out prominently tortuous and rigid, as in Case I. The eyes are rather prominent and the face thin. All the muscles of the body are extremely small, simulating a dystrophy. The arms, for example, would be small for a child. There are certain nervous symptoms of an atypical character. There is not paralysis, but a decided myasthenia. The gate is shuffling and unsteady, as if rather from a lack of confidence than from any real ataxia; deep reflexes are normal. There are no sensory disturbances. Her ideation is not normal, and yet it is not easy to give it a definite characterization. There is a tendency to fads, eccentricities, and fixed ideas. For example, she will no shake hands with anybody, on the theory that germs of disease are conveyed in that way. She is extremely difficult to influence, owing to her ideas. She lives a life of exclusiveness; in other words, she presents what one meets with in arteriosclerosis at times. The cranium is conspicuously enlarged, the hypertrophy of the bone being the most marked on either side in the parieto-occipital region. The frontal bone is also prominent. The head gives the impression of being too large for the face. The patient is not aware of this enlargement of her head, but I am told that it has existed for some twenty years (?). The cervicodorsal spine is rigid, as if ankylosed The long bones are small, as if atrophic, like the muscles, but not bent abnormally. She is free from pain and other symptoms, excepting that she is slightly deaf. The eyes were not examined. It was difficult to obtain a complete examination, which was, therefore, somewhat limited, and not as thorough as could be wished.

Whether such a case as this should be classified with hyperostosis, and not as an incomplete case of osteitis deformans, is difficult to answer in the absence of any fundamental criterion. The hypertrophy of the cranium without involvement of the long bones gives a striking resemblance to hyperostosis cranii; while the kyphosis and apparent ankylosis of the spine, giving the effect of a spondylitis deformans, the generally impaired nutrition, and the arteriosclerosis are suggestive at least of osteitis deformans.

Putnam, in his excellent monograph on hyperostosis cranii, somewhat summarily dismisses the question of the possible identity of this disease with Paget's, as do almost all writers on Paget's disease, on the ground that the latter affects the long bones and is a disease of advanced age. It seems to me that each succeeding writer passes over this question somewhat cursorily, without due consideration, as if the idea of non-identity were handed down as a transmittendum from the earlier writers.

In addition to Putnam's collection of fourteen cases of hyperostosis cranii, I have been able to find six others reported to date by Horsley,[1] Ellis,[2] Priestly,[3] Sattler,[4] Parker,[5] and Roberts,[6] respectively. These, with the above case of my own, make twenty-one.[7]

Of these twenty-one cases ten apparently began after thirty years of age and four after forty; and, conversely, of Packard, Steele and Kirkbride's collection of sixty-six cases of osteitis deformans in eleven the disease began before the age of forty. Moizard and Bourges report a case in which the onset occurred at twenty-one years, and Blanc reports one beginning at seventeen years, but in this last the accuracy of the diagnosis is not above suspicion. At any rate, considering the small number of cases of hyperostosis cranii on record, the age limit seems to be hardly a sufficient criterion.

As to the non-involvement of the *long bones*, Bowlby and Edmunds have each reported a case claimed to be osteitis deformans in which only one long bone alone was affected, and Hutchinson a case in which only two long bones were affected. In Bowlby's case the histologic examination showed changes resembling those described by Paget, so that if the disease may be limited to one bone it is logically possible that it may be limited to the cranium, which is so often and early affected.

It has been argued that a distinction between the two diseases is to be found in the hypertrophy of the malar bones in hyperostosis cranii giving the leonine appearance (leontiasis ossea); but this is not always found in this disease, and, conversely, a careful examination of recorded cases shows that the bones of the upper face are not always unaffected in Paget's disease.. For example, besides

[1] Practitioner, London, 1895, iv. 12-25.

[2] Archives of Ophthalmology, 1899, xxviii. 4.

[3] Quarterly Medical Journal, Sheffield, 1898, vii. 154.

[4] Cincinnati Lancet-Clinic, 1897, and Transactions of the American Ophthalmological Society, 1900. In the second paper the autopsy is reported.

[5] Annals of Surgery, 1894.

[6] Ibid., 1896.

[7] Ten other cases described under this title are to be found in the literature, but with insufficient evidence of the nature of the disease. Under hyperostosis cranii a variety o diseases has been included, from mere local tumors to a diffused condition, which later observation has shown to be osteitis deformans or some other process. In the absence of any definite criterion I have been perhaps somewhat arbitrary in the exclusion of questionable cases. Perhaps future investigations may show that some of these may be varieties of the disease in question, but at present it would seem to be wiser to limit our study to typical cases. I, therefore, only include those cases in which the bones of the head have been more or less diffusely affected.

minor hypertrophic changes, like hypertrophy of the superior alveolar border found by Joncheray[1] and Meunier,[2] and of the inferior orbital arches in two cases recorded by Lunn,[3] Meunier found hypertrophy of the malar bones giving the appearance of leontiasis ossea in a typical case of osteitis deformans. Likewise, Gilles de la Tourette and Magdalaine[4] report a similar hypertrophy of the malar bones, as does Pic;[5] so that the presence or absence of this particular hypertrophy would not seem to have the importance ascribed to it.

From the point of view of pathologic anatomy the differentiation of the two affections is equally difficult. In hyperostosis cranii the anatomic findings have consisted of new bone tissue in which calcification has taken place both in the surface layers and in the diploe, so that the latter is converted in some cases into a coral-like tissue; in others into a hard tissue like ivory, as was found in a case of my own. Actual softening does not seem to have been observed excepting in a case reported by Stack;[6] but I know of no case in which a histologic examination was made, and, therefore, we can only surmise that, as in osteitis deformans, an absorptive process may have produced the sponge-like spaces in the hypertrophied diploe.[7]

Stack's case, which I have not included, because it is not clear that it is not a complication of hyperostosis with osteomalacia, should be studied in this connection, for if the softening of the long bones is not a complication the case is a transition between the two types we are considering. At the autopsy the skull was found to be enormously and almost uniformly thickened. All the cranial bones were affected, including those of the face. The cerebellar portion of the skull was very protuberant, dipping down toward the neck, and measured here in thickness almost three inches. The bones of the skull on section were for the most part softer than natural, but the appearance was not quite homogeneous. In parts there were masses of more compact tissue, and in others the rarefaction had proceeded to

[1] Paris Thesis, 1893.
[2] Nouvelle Iconographie de la Salpêtrière, 1894, t. vii. 17.
[3] Trans. Clin. Soc., London, xviii. 273.
[4] Nouvelle Iconographie de la Salpêtrière, 1894, t. vii. 1.
[5] Rev. d'Orthopedie, May 1, 1897, viii. 164.
[6] Bristol M. C. J., 1900, xviii. 316–320.
[7] Four cases of Horsley (Practitioner, 1895) reported under the titles of leontiasis ossium ought not to be overlooked entirely. The hyperostosis was of the nature of a bone tumor, and was removed by operation. Histologic examination of the removed bone in two showed the presence of a process which was both absorptive and osteoplastic.

such an extent as to leave spaces of an eighth of an inch in diameter. The half skull without the lower jaw weighed seven pounds and a half. The lower jaw weighed one pound. The pelvis was very light, very soft, and much distorted; it was markedly generally contracted, scoliotic, funnel-shaped, and beaked. The femora were both bent and a little softer than natural. The tibiæ were also bent, and in some places the external compact layer was replaced by softened bone developed from the periosteum. There was no overgrowth in any bone apart from the head. It will be noticed that the rarefying process resembles in the description that of osteitis deformans.

Now, although in numerous histologic examinations of the bones in osteitis deformans the findings have been similar to those described by Packard, Steele and Kirkbride, this would seem to be not the whole story, for more or less calcification may take place in the new bone tissue, so that patches of greater or less extent of ivory-like density occur.[1]

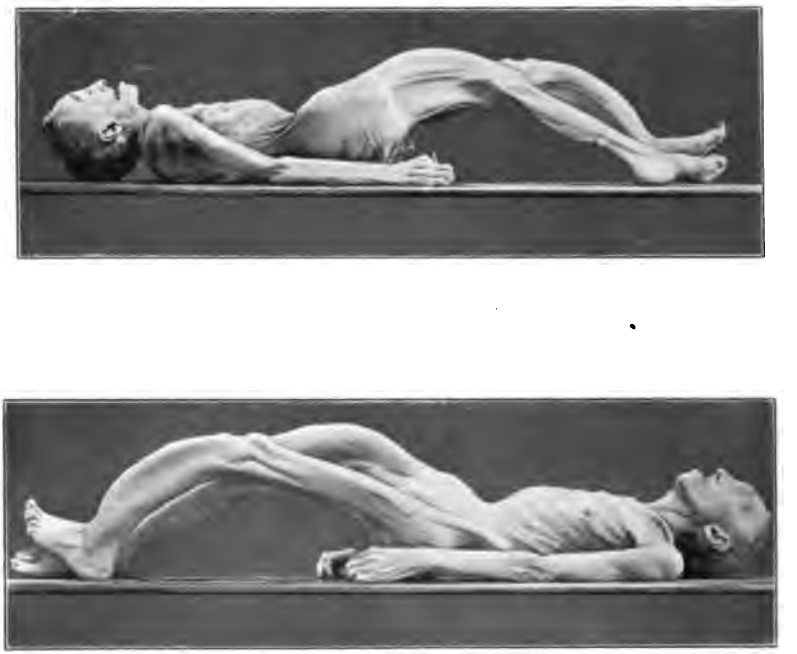
Not a few autopsy findings in which the formation of new bone with calcification is the chief process might be easily cited. The fact is, whether absorption predominates or new bone formation, without calcification or with calcification, is probably either a matter of stage in the process or dependent on unknown determining factors. At any rate, as a matter of observation, one process may predominate in one bone and of the other process in another in the same case. The autopsies, then, thus far made describe a combination of anatomic

[1] Paget, in describing the findings in his first case, states that "the compact substance of the bones was in every part increased in thickness." "In the greater part of the walls the whole construction of the bone was altered into a hard, porous, or finely reticulated substance, like very fine coral. In some places, especially in the walls of the femur, there were small, ill-defined patches of pale, dense, and hard bone looking as solid as brick. In the compact covering of the articular ends of the long bones . . . the increase of thickness was due to encroachment on the cancellated texture, as if by filling its spaces with compact porous new-formed bone." Microscopic examination confirmed the macroscopic findings of new bone formation, with calcification. Bowlby describes similar changes in a femur, the only bone affected, remarking upon the formation of "new bone, sometimes of a hard, porcellanous appearance, and again of a more cancellous nature." Bowlby's case may be questioned as a true example, owing to only a single bone being affected, and yet the similarity of the changes to those found by Paget should be noted. Silcock, in an important observation, states that in a femur the superadded bone was everywhere compact and ivory-like excepting at one spot.

Lunn, again, while describing changes identical with those found by Packard, Steele and Kirkbride, also notes in addition the formation of calcified bone, which, as parallel lamellæ, reduced the size of the Haversian canals to the smallest caliber.

Equally important in showing calcification is the chemical analysis, which demonstrates substantially no deviation from the normal amount of lime salts in the bone (Paget) and even an increase (Robin, Gilles de la Tourette, and Magdalaine).

FIG. 5.



Sophia D., aged 73. Osteitis deformans. From a photograph kindly sent me by Mr. J R. Lunn, F.R.C.S.

processes which may be briefly stated to be: (*a*) Absorption of bone; (*b*) new formation of bone tissue without calcification; (*c*) new formation of bone tissue with calcification. Any of these processes may predominate.

It is an interesting fact, to which attention has not been called in this connection, that in young, healthy-growing bones an allied process takes place. The bone tissue around the Haversian canals may be absorbed, as in osteitis deformans, even to the extent of producing "irregularly bounded cavities of varying size with eroded edges, and lamellæ appearing as though gnawed away at points." Thus are formed the Haversian spaces. Reformation of new bone may then take place and fill up these spaces (*Frey's Histology*). This process is plainly a normal trophic one. This would suggest that it is within the bounds of possibility that the process in osteitis deformans is a modification or perversion of the same process which is provided for by nature in normal bones. Under such an hypothesis it would be a nutritive or trophic disorder.

In hyperostosis cranii it is possible that the anatomic process may be the same as in osteitis deformans, only that the process of calcification has predominated, and hence the greater density of the bones of those skulls examined in this disease as compared with the bones examined in osteitis deformans. But it must be borne in mind that very few cases of hyperostosis cranii observed during life have come to an autopsy, and of these none have been submitted to microscopic examination, and in none, unless Stack's can be accepted, have any of the long bones been examined either macroscopically or microscopically; so that, after all, we have no positive knowledge that the long bones have not to some degree participated in the process. Then, too, in Paget's disease very few bones in any one case have been histologically examined; but, as the facts stand, of the bones examined in the same case one or the other has shown considerable calcification, while another has shown less. The evidence thus far is too fragmentary to allow us to form a definite conclusion based on the anatomic findings alone. (Fig. 5.)

CASE III.—Since the above was written—that is, last Friday—I had an opportunity, through the kindness of Dr. Edes, to re examine the case which he reported in 1896[1] under the title of hyperostosis cranii. I find that this

[1] American Journal of the Medical Sciences, July, 1896.

case has developed into one of Paget's disease. Since 1896 the hypertrophic process in the head has greatly increased, as may be seen by comparing the photographs. (Figs. 6 and 7.) *Almost all, if not all, the long bones of the body are affected.* The right humerus is particularly deformed in a characteristic way, as is shown in the accompanying skiagram. There is kyphosis in the lower dorsal region and deformity of the sternum. (Fig. 8.) The clavicles have escaped. The attitude of the patient is characteristic. What is of particular interest is that some of the phalanges of the fingers show traces of the disease in that they are bent, and the bones of the tarsus of one foot appear to be thickened. Then the nervous system shows certain abnormalities. There is general myasthenia, amounting to a paresis. The gait is paretic and unsteady, so that she requires help to maintain her balance in walking. She has a tendency to fall, not due to the paresis; but no true ataxia can be made out, and Romberg's symptom is absent. The tactile and pain senses are normal; the knee-jerks are exaggerated. Plantar reflexes are absent. She has marked difficulty in swallowing, so that, for example, a glass of milk was drunk with great slowness and caution. The tongue protrudes straight; the face moves more to the right than to the left in speaking. The eyes are protruding, and there is a twitching of the right upper eyelid. There is decided deafness. There is no evidence of arterial atheroma, but there is an aortic systolic murmur. It is difficult to ascertain the exact time of development of the disease in the long bones. The patient says that her own attention was not called to these changes until after she had been observed by Dr. Edes, who tells me that he does not remember having made an examination of the limbs. It is possible, therefore, that the long bones may have been affected before 1896.

This case suggests the possibility that some of the other reported cases of hyperostosis cranii either may have developed later into Paget's disease, or that, if they had been more critically examined, the long bones would have been found to have been affected. As a matter of fact, in very few instances is any specific reference to the long bones made in the reports, and it is doubtful if they have been often examined.

No reference to the long bones is made in Putnam's observations, and it is probable that they were not examined, as they were not in my own first case.

Osteoarthritic Changes. The frequency with which osteoarthritic changes are found in Paget's disease has not received the attention which they invite. These changes are identical in character with those found in certain types of rheumatoid arthritis, or, perhaps more correctly, osteoarthritis. They are always regarded as evidences of co-existing rheumatoid arthritis rather than as different manifesta-

FIG. 6.

CASE III. Mrs. W., 1896. From Edes' article.

FIG. 7.

CASE III. MRS. W., 1902. Osteitis deformans, formerly thought to be hyperostosis cranii. Compare with Fig. 6, which is the same case photographed in 1896.

tions of the main pathologic process. There are many facts which tend to show the incorrectness of this view.

In the first place, the frequency with which osteoarthritic changes occur suggests some sort of kinship between this process and that in the body of the bones rather than the coincidence of two separate diseases.

Richard pointed out what he called transition cases between the two diseases. Humphrey calls particular attention to the presence of the two diseases in his specimens of a femur and tibia, as does Bowlby, who, in describing the appearance of the femur already referred to, specifically states that "some parts of the head and neck present changes exactly similar to those noted in an early stage of rheumatoid (osteo) arthritis, the bone being smooth and porcellanous, with growth of nodosteophytes and with the worm-eaten appearance so common in this disease." In one of Stilling's cases von Recklinghausen found arthritis deformans at the autopsy. Goodhardt, in one case, describes deposits of new bone along the bodies of the vertebræ anteriorly, resembling in the description spondylitis deformans. In another case Goodhardt states that "bones of hard new-growth projected slightly from the substance of the bodies and welded the bones together by a tough, tuberculated mass, which looks not unlike the nodular masses found in some extreme cases of osteoarthritis when that disease attacks the spine." Equally if not more remarkable findings in this particular, however, are those of Lunn, who describes a condition of the vertebræ exactly similar to that characteristic of spondylitis deformans of the type we are considering. "Projecting from the sides of some of the bodies of the vertebræ (chiefly lumbar) were well-marked bosses of new bone with disappearance of the intervertebral disks, and bony ankylosis had taken place at different intervals."[1]

The rigidity and ankylosis of the spine, which clinically is frequently observed in Paget's disease, undoubtedly is often, though not necessarily, due to a condition identical with that found by Goodhardt and

[1] Compare this with the following description of Goldthwait from his article on "Spondylitis Deformans, or the Spinal Form of Osteoarthritis:" "Pathologically, the disease consists of a nodular enlargement of the edges of the articular cartilages, with the subsequent ossification of these nodes and an extension of the process into the ligaments which have their origin or insertion near by. With this hypertrophy at the edges of the cartilage the centers or areas of pressure usually undergo atrophy." . . . "As the process continues either the two surfaces of bone fuse or remain in apposition."

Lunn, and described by Goldthwait in his monograph referred to. Clinically, also, ankylosis of the larger joints is not infrequently observed in Paget's disease, a process which it is hard to explain by the absorptive and formative processes peculiar to osteitis deformans proper, and is probably due to the osteoarthritic processes found at autopsies.

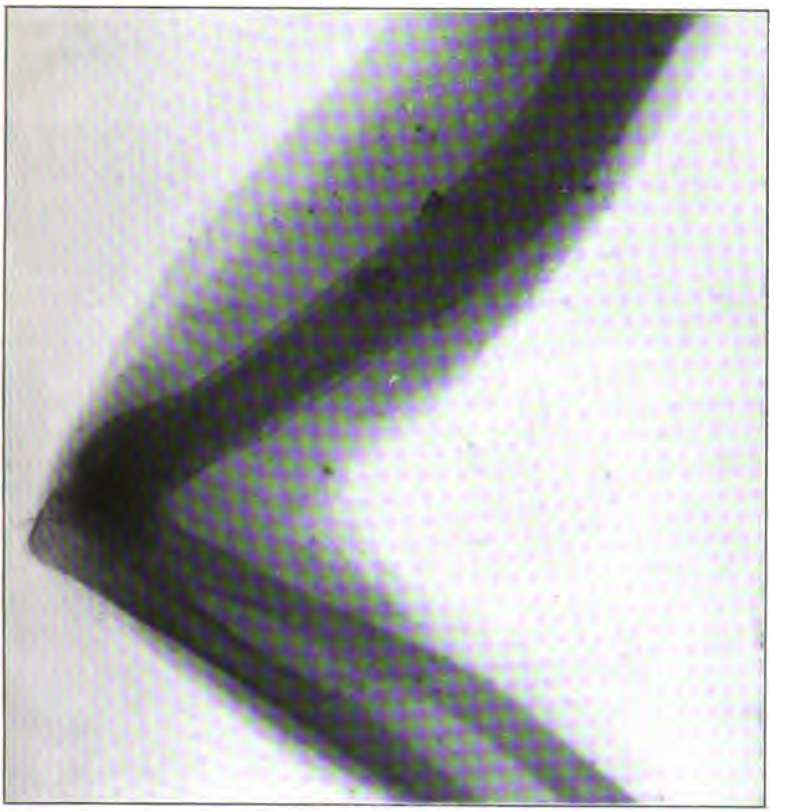
In my case nodosities are present in some of the phalangeal articulations, strongly suggestive of osteoarthritis. In three of Lunn's cases ankylosis of the larger joints was present, and in a fourth there were bony growths about the knee-joints.

When we consider the variations in the anatomic processes found in osteitis deformans there does not seem to be any good reason for regarding these osteoarthritic changes as anything more than a predominance of the hypertrophic process which is observed in the bodies of the bones, a view which will receive support when we come to consider the disease as a trophic derangement.

In hyperostosis cranii, as well as in Paget's disease, the vertebræ sometimes take part in the hypertrophic process, or at least this seems to be the case from what can be made out during life. At any rate, fixation of the spine (my case) and thickening of the vertebræ can be felt (Starr).

Special Pathology. Baumgarten, Starr, and Putnam have insisted that hyperostosis cranii is a trophic disorder, while several writers have done the same for Paget's disease. The thought suggests itself whether all the bone lesions commonly found associated in osteitis deformans and hyperostosis cranii, including those referred to rheumatoid arthritis, different as these anatomic lesions are, may not represent only perversions of a central trophic arrangement analogous to the so-called trophic lesions observed in spinal and nerve lesions. But when we attempt to point to any particular derangement, whether in the nerve system or elsewhere, we are made conscious of the blindness of our knowledge. And yet there are a number of facts which may have a bearing at least on the solution of the problem. So far as concerns the possibility of a central nervous derangement being capable of producing the osseous changes, the lesions in tabes and syringomyelia are instructive. In these diseases as well as some others affecting the central gray matter there is a very remarkable tendency to calcification or ossification of the ligaments and absorption of the cartil-

FIG. 8.



CASE III. Osteitis deformans; right arm.

ages of joints and development of bony masses about them—changes which in themselves have a very close resemblance at least to what occurs in osteoarthritis. Then, again, the process may be one of rarefaction or hypertrophy, and either may predominate. In the latter case the shaft of a long bone may undergo an extraordinary increase in size by the development of new osseous tissue on the surface. Further than this, deformities of the skull occur in syringomyelia, characterized by bossing of the frontal and parietal eminences and prominence of the forehead.

A very remarkable case was published by Hale White[1] under the title of "Hyperostosis Cranii." Later the case came to autopsy as the result of operation for fits, and was described by Collier. Unexpectedly a condition of syringomyelia[2] was found, which did not give rise to the ordinary sensory symptoms of that disease, although there was a spastic atrophic paralysis of one arm of obscure origin, but thought before death to be cerebral. The skull was very remarkable. The deformity which had been taken for a hyperostosis was a projecting ridge or fold extending from the temporal region on each side backward around the occiput and overhanging the neck. It was as if the spine and base had been telescoped into the skull, which overhung the base like a mushroom.

The bones of the skull were for the most part small, and in some places thin, but in other places they were "unduly large" (hypertrophied?). The deformity had begun in childhood, and was supposed to have followed a fall upon the head.

The nature of the bone changes is not clear, but it was apparently one of perverted nutrition, and very likely connected with the syringomyelia as one of the trophic lesions of that disease.

The combined anatomic picture presented by these lesions in nervous diseases is very different, of course, from that seen in Paget's disease, but the individual processes suggest the variety of changes which may be brought by one and the same nervous derangement. Several writers have suggested that the *fons et origo* of Paget's disease

[1] British Medical Journal, 1896, vi. 1377.

[2] Lancet, January 5, 1901. The cavity extended from the left inferior olivary downward in the posterior horn to the sixth dorsal, excepting that it intermitted from 8 c. to D 4; marked old degeneration in the right pyramidal (tract?), which could be traced to lumbar region. Nerve cells normal by Nissl method; brain normal. Report too incomplete to allow the cause of the arm paralysis to be determined.

was to be found in the nervous system. Stilling, in 1889, attributed the coexistence of the two diseases to coincidence, and this view has been repeated successively by later writers. The possible dependence of osteitis deformans upon some kind of nervous lesion, it seems to me, has been rather hastily discarded without due consideration of the facts, and perhaps without a critical examination of the original records. Sometimes it has been taken for granted that the autopsy findings have negatived such an hypothesis. One of the later monographs states that "the results of many examinations . . . have shown the cord and bone nerves . . . to be perfectly normal."

This seems to be a hardly well-considered statement. I have not been able to find that the spinal cord has been examined at all, excepting in ten cases, and in five of these there was more or less evidence of pathologic changes. In three (Gilles de la Tourette and Marinesco two, Levi one) a gross lesion in the form of posterior sclerosis was found under the microscope. In one, that of Pic, the spinal cord, to the naked eye, showed a grayish tint in the two posterior columns and in the right pyramidal tract. In one case (Stilling) some, though not marked, changes were found by von Recklinghausen, viz.: there was a small gliomatous growth in the cervical region and sclerosis of the ependyma. To the naked eye the gray substance throughout the whole length of the cord was white, opaque, and not easily distinguishable. The import of this is not mentioned by the reporter, but the ganglion cells and nerve trunks under the microscope appeared to be normal. It is suggestive that this case exhibited contractures and muscular weakness, if not paralysis, which must have been of spinal origin. In the sixth case, that of Lunn (*Trans. Clin. Soc.*, vol. xviii.), the spinal cord was found to be "soft in the cervical region, almost pulpy opposite the first and second dorsal and seventh cervical vertebræ." "A year before the patient died he developed symptoms of bulbar paralysis, with extreme wasting of the tongue, dysphagia, and some loss of taste. *No microscopic examination was made.*" It is evident that the cord softening, from its situation, was something in addition to the bulbar disease.

This leaves four cases to be accounted for. In two of these four (Stilling, Noizard, and Bourges) there was no microscopic examination of cord or nerves at all, but in the remaining cases, two, the microscopic examination showed the cord and nerves to be normal.

Of ten cases, then, there was more or less good evidence of disease in six, not examined microscopically in two, and normal in two only. It does not appear that in either of the normal cases (Stilling and Goodhardt) any of the finer methods of technique were employed, including the special stains. One was examined as far back as 1878 (Goodhardt). The report of this simply states that "the spinal cord was quite healthy, both to the eye and under the microscope." The nerves were not examined. We must also bear in mind that we do not know what cells or elements in the cord, if any, regulate the nutrition of the bones, so that we do not even know where to look for the lesions which may be responsible for bone and arthritic changes. Therefore, it well may be easy to overlook them, as, indeed, the history of many originally obscure nervous diseases shows. At any rate, from this examination of the reports of autopsies it would appear that the frequency with which changes have been found in the nervous system has been overlooked. More opposed to the nervous origin of the disease is the fact of entire absence of nervous symptoms in the mass of cases. But this objection, it seems to me, is based on a too superficial view of the question. In the first place, as I have said, we know almost nothing of the seat of the trophic functions of the cord beyond the fact that lesions of the anterior cornua lead to muscular atrophy, and we are entirely ignorant of what elements in the cord subserve nutrition of bone or skin and other organs. Even in tabes we are ignorant of the special lesion which causes the trophic changes in the bones, whether seated in the anterior or posterior portions or in the peripheral nerves. *It is not inconceivable that as degeneration of the anterior cornua may cause myopathies without other symptoms, so lesions of other special cell groups may cause osteopathies without other spinal symptoms.* In the second place, it is a curious but interesting fact that in neither of the two cases of Gilles de la Tourette nor in that of Levi, in all of which an extensive sclerosis was found, were there any recognizable nervous symptoms during life, not even absence of knee-jerks, excepting that in Levi's case there was diminution of intelligence, ready weeping, and binocular nystagmus, and at the end only incontinence of urine and feces.

But it is exceedingly improbable that the lesion, if it is to be found in the nervous system, is that of one of the stock nervous diseases. If such were the case we should expect to find the bone lesions occur-

ring from time to time as manifestations of one or more of these diseases. It is much more probable that the pathologic changes may be of a more general and finer type, such as would interfere with nutrition alone. Perhaps the arterial sclerosis which almost always is found, and which sometimes is so extraordinarily obtrusive in the younger cases, may be the primary source of nutritional changes. In the first of Gilles de la Tourette and Marinesco's cases the sclerosis of the posterior columns did not extend below the dorsal cord (the cervical cord was overlooked), and some of the fibers in the lateral columns were diseased. (The nerves were not examined.) In the second case, beside the sclerosis of the posterior columns most developed in the dorsal region, the peripheral nerves were the seat of an interstitial neuritis. The authors do not consider that the disease in the cord was a true posterior sclerosis, but rather an atrophy of nerve fibers. Levi also insists that the extensive sclerotic changes, with disappearance of myelin fibers that he found in both posterior and lateral columns and other regions, were to be regarded as a pseudosystemic sclerosis of vascular origin. The vessels throughout were the seat of a periarteritis and endarteritis. The spinal nerves showed irregular thickening of their connective tissue; the sciatic showed practically the same changes that were found in the cord.

It would seem to be highly possible that as a result not of a posterior sclerosis or a lateral sclerosis, but of the vascular sclerotic changes that are always or almost always found in osteitis deformans, nutritional impairment might be brought about in the central nervous arrangements which we have to suppose govern the nutrition of the bones, just as the anterior cornua govern the muscles, and that future researches may reveal the nature and seat of these changes. In emphasizing this hypothesis I do not overlook the fact that in old people changes in the nervous system are apt to develop, and that the occurrence of these changes with bone lesions may be a coincidence.

What I have said is mostly speculative; but, considering the absolute blindness of our knowledge of osteitis deformans and the completely negative position in which the subject has been left by all writers on the subject, I have thought it might not be without value to put together the allied facts in our possession, hoping that they might furnish a working hypothesis and point the way for further

pathologic investigation, by which alone we can understand this most remarkable disease.

By way of summary, then, I would say:

1. We have no sure ground for differentiating hyperostosis cranii from osteitis deformans.

2. Hyperostosis cranii and osteitis deformans are probably trophic disorders.

3. Various clinical and pathologic facts seem to indicate that they are at least allied disorders, and perhaps only different manifestations of one and the same disease.

4. The osteoarthritic changes so commonly found in osteitis deformans are probably manifestations of the disease, and not complications.

5. The results of autopsies thus far made do not at all exclude the nervous system as the seat of the trophic derangement; but the changes that have been found in the spinal cord and peripheral nerves and analogy with other known lesions like those of tabes and syringomyelia suggest a neuropathic origin similar to that of the myopathies.

6. In future cases the nervous system should be exhaustively studied.

[NOTE.—I wish to express my obligation to Dr. Packard for his great kindness in loaning me his references to the literature and abstracts of reported cases, thus materially aiding this study.]

CERTAIN CHARACTERISTICS OF OSTEITIS DEFORMANS.

By REGINALD H. FITZ, M.D.,
OF BOSTON.

The first case reported by Dr. Prince subsequently came under my care at the Massachusetts General Hospital, having been referred to me by Dr. M. A. Morris, of Boston. There are certain points of interest resulting from my study of the patient and the disease concerned which I desire to place on record, even at the risk of duplicating some of the observations which Dr. Prince may have made.

These concern especially the recognition, by means of the Röntgen rays, of the alterations of the bones and the intimacy of the relation between cranial hyperostosis and osteitis deformans.

In this connection I wish to acknowledge my indebtedness to Mr. Walter Dodd, of the hospital, for the photographs and skiagraphs which will illustrate my remarks, and especially for his expert assistance in the interpretation of doubtful points in the latter series of pictures, and in establishing the conclusions to be drawn from them.

I am indebted also to my assistant, Dr. R. F. Gibson, for his aid in obtaining the completest possible record of the case, which is offered as a supplement to that of Dr. Prince.

The patient was born in Boston, in and near which she has always lived. Entered the Massachusetts General Hospital February 6, 1902. Her father died of phthisis, aged eighty-four years; her mother died of the same disease at fifty-eight. Has two sisters, of thirty and thirty-eight years, respectively; both well. Has four living, healthy children. One died of unknown cause soon after birth. Has had measles, scarlet fever, and whooping-cough early in life, and seven years ago states that she had typhoid fever. Menopause at thirty-six. Has not used alcohol, but has drank much tea until a year ago. Her average weight is 110 pounds.

Two years ago, when in her usual health, it was noticed that the right forearm was curved, and she attributed this condition to wringing clothes in her laundry work. A year ago, while walking, had three or four attacks of vertigo, each lasting a few minutes. These ceased at the end of a fortnight. Ten months ago she began to feel weak and tired and had occasional periods of drowsiness. At this time there was slight, constant pain at the top of the head and in the occiput. She was able, however, to keep at work.

Five months ago, at the Boston City Hospital, she came under the observation of Dr. M. Prince, who first made her conscious of any peculiarity in her appearance, which, in her own opinion, has not since changed.

In January, 1902, she consulted Dr. M. A. Morris, of Boston, in consequence of severe pains throughout the head of some six weeks' duration, although temporarily replaced for a day or two on one occasion by pains in the left shoulder and hypochondrium. She complained also of digestive disturbances, which had been more or less troublesome for three or four months. At this time she considered her strength unaffected. Dr. Morris recognized her condition as one of osteitis deformans, and referred her to me, with the view that she should receive such opportunity for study and observation as the hospital might afford, and that she might attract the attention of medical students.

At the time of her entrance she complained of pain throughout the head and of sharp, shooting pains in the back, hips, arms, and legs. She was disturbed by gas in the stomach and bowels after meals. Pulse, 100; respiration, 20; temperature, 98° F. Weight, 99 pounds.

The cranium appeared large in all diameters, especially from before backward and from above downward. The occiput bulged and the temporal ridges were extremely prominent. The mastoid portion of the temporal bones was conspicuously large. There was marked enlargement of both malar bones and of the right lower jawbone. The other bones of the face were not enlarged. The hair of the scalp was coarse and dry, and bald spots were numerous.

Many of the teeth were gone from the upper jaw and several from the lower jaw. Caries was frequent in those present. The temporal arteries were markedly tortuous and thickened and lay upon the surface of the bone.

There was pronounced kyphosis, with inability to straighten the curved portion, although elsewhere there was fair motion of the spine. The patient was pigeon-breasted, and the xiphoid cartilage was thickened and unyielding. The right clavicle was slightly enlarged, and there was enlargement of the acromion process and the spine of the right scapula. The crests of both iliac bones were thickened. There was some thickening of the right humerus and extensive upward and backward curvature, with thickening of both bones of the right forearm, the pronation of which was limited. The distal phalanges of each hand were somewhat thickened. There was extensive thickening of both thigh bones, with curvature forward and outward. Both tibiæ, especially in the upper third, were markedly thickened, and were curved forward,

a change more marked in the right than in the left leg. The epiphyses were enlarged, the motion of the joints was not impaired, and there has never been any complaint of pain or stiffness in any joint or tenderness in any bone.

The following measurements were made by Dr. Gibson: Height, 57 inches; circumference of head, 24½ inches; distance from zygoma to zygoma over top of head, 13 inches; breadth between temples, 4¼ inches; distance from root of nose to point of chin, 4⅝ inches. Girth of right arm 3 inches above bend of elbow, 7⅝ inches; girth of left arm 3 inches above bend of elbow, 7½ inches; girth of right forearm 3 inches below epicondyle, 7½ inches; girth of left forearm 3 inches below epicondyle, 7 inches; girth of right thigh 6 inches above upper edge of patella, 16 inches; girth of left thigh 6 inches above upper edge of patella, 15½ inches; girth of right calf 5½ inches below lower edge of patella, 12½ inches; girth of left calf 5½ inches below lower edge of patella, 12½ inches.

The area of cardiac dulness was somewhat enlarged both to the left and right of the sternum. The apex-beat was diffused and heaving, most marked in the left fifth interspace 3½ inches from the median line. There was a systolic murmur in the aortic area, transmitted into the neck, and a harsh, systolic murmur in the mitral area, replacing the first sound and transmitted toward the axilla. The pulmonic second sound was accentuated. The action of the heart was somewhat irregular in force and rhythm. The radial arteries were thickened and ribbed, and the brachial arteries were thickened and tortuous. The volume and tension of the pulse were good in the right wrist, but diminished and obtained with difficulty in the left wrist.

The examination of the blood showed 80 per cent. of hemoglobin, 4,450,000 red corpuscles, and from 7000 to 10,000 leukocytes. The differential count of the latter gave 70 per cent. of polynuclear leukocytes, 18 per cent. of small and 4 per cent. of large lymphocytes.

The examination of the lungs and abdominal organs was negative. The urine was acid, 1020, contained neither albumin nor sugar, and the sediment was not pathologic. At one examination, however, the slightest possible trace of albumin and a rare granular cast were found. The pharyngeal reflex was absent, but the pupillary, patellar, and plantar reflexes were present and normal.

The eyesight has been failing somewhat for the past two years, and glasses have been worn with relief for five months. There is no impairment of hearing. The sense of touch is unaffected; there are no paresthesiæ, and the appreciation of heat and cold is normal. There is less sweating than formerly, but the skin is soft and smooth. The loss of hair began nine months ago, and persisted for six months; she thinks that nearly one-half is gone. There is no loss of hair except from the scalp. The finger-nails show no alteration.

When the patient entered the hospital there was an evident impairment of mental function; her answers were intelligent and direct, but at the end of three days she left her bed at night and wandered from the ward, expressing

PLATE I.

Hyperostosis of first phalanx of thumb, fourth metacarpal and carpal end of radius. Osteoarthritis of terminal phalanges. Calcification of arterie of arm and hand.

Normal hand.

Normal foot.

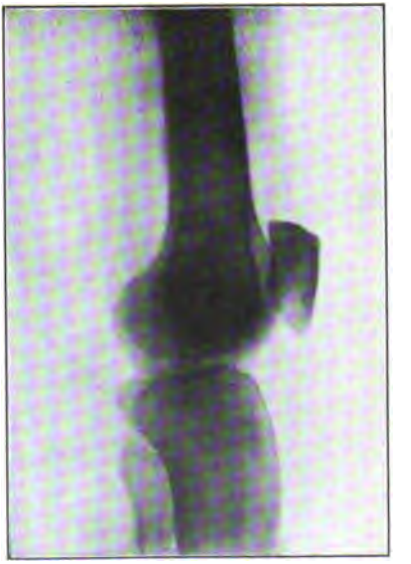
PLATE II.

Right. Left.

Right. Hyperostosis of all metatarsal bones except the third. Foci of decalcification of first and third. Absence of trabecular structure in second contrasted with its persistence in the fifth metatarsal.

Left. Hyperostosis and decalcification of first phalanx of great toe. Hyperostosis and decalcification of all metatarsal bones except the filth.

Right femur from inner lateral surface. Hyperostosis of femur, extending into epiphysis. Cortical thickening; erosion of anterior surface of femur. Hyperostosis of patella, decalcification and coarse trabeculation.



Normal.

PLATE III.

Left ankle and lower two-thirds of leg. Hyperostosis and decalcification of the tibia, fibula, astragalus, and os calcis. Coarse trabeculation, lamellar thickening of tibia and fibula.

Normal.

PLATE IV.

1

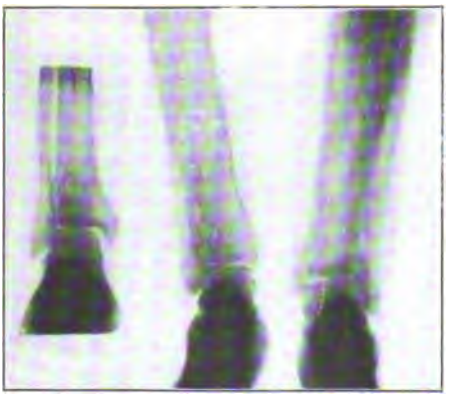
1. Hyperostosis of tibia, astragalus, os calcis, cuboid, and internal cuneiform. Decalcification and coarse trabeculation especially apparent in os calcis.

2

2. Normal.

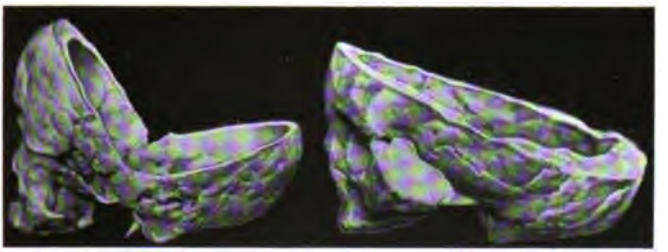
3 4

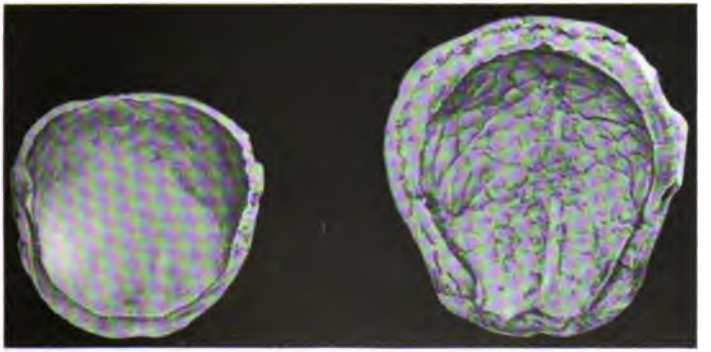
Right. Left.



3. Normal. 4. Hyperostosis of both external malleoli; extensive decalcification; disappearance of right internal malleolus.

PLATE V.





Osteitis syphilitica (?). Hyperostosis.

fear that her eyes were to be taken out; the latter had been examined ophthalmoscopically a day or two before. She remained in the hospital nearly four weeks. During this time she gained some four pounds in weight, her pains lessened, but she was more or less restless at night, at times screaming or attempting to leave the ward, or threatening to injure herself in consequence of delusions with regard to her children. She believed them dead, and when visited by them stated that the visitors merely simulated the children, although wearing their clothes. She heard imaginary conversations; and complained that the nurse did not give the right medicine and lied about her. She thought some dreaded operation was to be performed, wept occasionally, and talked constantly about her troubles and ailments. In consequence of the persistence of her delusions and the inability of her family to take care of her she was transferred to the Boston Lunatic Hospital.

To recapitulate: a healthy, hardworking woman at the age of forty-three years became aware of a curvature in the right forearm. A year later there were temporary attacks of vertigo for a short time, which soon were followed by pains in the head, drowsiness, and debility. Five months afterward her cranial deformity was first called to her attention. At present there is hyperostosis of the cranium, malar bones, right inferior maxilla, clavicle, scapula, humerus, radius, ulna, iliac crests, femora, and tibia. There were also kyphosis and pigeon-breast.

The case evidently is one of osteitis deformans, with conspicuous cranial hyperostosis complicated with rheumatoid arthritis, arterial degeneration, chronic valvular disease, and, lastly, with mild melancholia accompanied by delusions.

The alterations of the bones in osteitis deformans, originally described by Paget (*Med.-Chir. Trans.*, 1877, lx. 87), are recognized as characteristic by later observers, and nothing essential has been added to his statement of them. The bones usually affected are those of the cranial vault, the spine, and the larger long bones of the extremities; less frequently the clavicles, scapulæ, ribs, sternum, and pelvis are altered, and, rarest of all, is mention made of changes in the bones of the face, hands, and feet. The enlarged bones are abnormally dense or rarefied. The surface is smooth or rough, nodular or protuberant; the cortex thickened or thinned, spongy or eburnated, the cancellated structure sclerosed or coarsely trabeculated, the marrow spaces obliterated or transformed into cavities of various size. The central canal of the long bones is narrowed or dilated, even to disappearance, and the deformity of these bones is further increased by various degrees of abnormal curvature. There is no uniformity in the distribution of these alterations, and a single bone may give evidence of the decalcification and absorption, the formation of osteoid

tissue and its calcification, which are the processes concerned in the production of the gross changes. Multiplicity of the bones affected is the constant characteristic.

Until within the past few years the closer study of the nature and distribution of these changes has been possible only by the examination of macerated bones and by the microscopic investigation of decalcified portions of certain bones. The information thus obtained is somewhat fragmentary, and necessarily limited to the conditions existing at a particular time, although early and late manifestations of the disease may be present at one and the same time. All writers call attention to the unknown period of latency, during which the existence of the malady is unrecognized, and the long term of years through which it slowly progresses. Any means by which periodical examinations of the alterations in the bones may be made promises to add very materially to our knowledge of the subject, especially with reference to the progress of the affection and to the conditions promoting curvature, and the future study of osteitis deformans and allied diseases in which the bones are involved must depend largely upon the use of the Röntgen rays. Watson (*Johns Hopkins Hospital Bulletin*, 1898, 133), Elting (*Ibid.*, 1901, 343), and Wilson (*Philadelphia Medical Journal*, 1902, ix. 322) already have illustrated their communications on osteitis deformans with skiagraphs. These show the degrees of enlargement and curvature of certain bones, and Watson in particular calls attention to peculiarities of structure. The accompanying skiagraphs, made by Mr. Dodd, still more satisfactorily indicate the value to be anticipated from the use of the Röntgen rays in defining the various stages in the progress of the disease, and they are contrasted with those obtained from normal bones for the purpose of ready comparison. They are a portion only of the series taken. (See Plates I. to IV.)

Mr. Dodd describes the alterations as follows:

"*Skull* much thickened, lower jaw greatly enlarged, coarse trabeculation and decalcification.

"*Clavicle* hyperostotic, the condition more marked in right than in left collar-bone.

"*Scapula.* Axillary border; acromion and coracoid process of right scapula hyperostotic, with foci of decalcification. A similar condition in the left scapula, but much less in degree.

"*Humeri* hyperostotic, with coarse trabeculation and decalcification. The alterations more extensive in the right than in the left humerus.

"*Forearm.* Right radius and ulna hypostatic, with decalcification; marked curvature of radius. Bones of the left forearm apparently normal.

"*Hands.* Terminal phalanges of each hand show the conditions found in osteoarthritis. The right hand shows hyperostosis of the third metacarpal bone, with area of decalcification; also marked hyperostosis of carpal end of the radius and ulna. In the left hand there are hyperostosis of the first phalanx of the thumb and a spicule of bone (?) at the inner border. The head and cortex of the fourth metacarpal bone apparently thickened.

"*Pelvis.* Hyperostosis and coarse trabeculation throughout the right os innominatum.

"*Right Femur.* Hyperostosis and coarse trabeculation throughout the shaft. The neck and head also involved, but to a less extent. Right patella also shows hyperostosis and coarse trabeculation.

"*Lower Leg.* Tibiæ hyperostotic, with coarse trabeculation and large areas of decalcification, more marked in the right than in the left tibia. Cortical thickening of the right tibia and fibula. Left internal malleolus almost wholly decalcified.

"*Foot (right).* Hyperostosis and decalcification of the astragalus, os calcis, and all the metatarsal bones except the third. Decalcification of the first and second metatarsal bones. Trabecular structure well preserved in the fifth, but absent in the first and second bones. The phalanges normal. The left foot shows hyperostosis of the astragalus, os calcis, cuboid, and internal cuneiform bones. Decalcification and coarse trabeculation are especially apparent in the os calcis. Hyperostosis of all the metatarsal bones except the fifth, which is apparently normal. The first phalanx of the great toe shows marked hyperostosis and decalcification. Other phalanges normal."

From the inspection of this series of skiagraphs it is evident that the various changes in the bones described by Paget are to be determined to a considerable degree in the living patient. The nature and extent of the involvement of individual bones is appreciable, likewise the discovery of similar changes in bones which hitherto have attracted but little attention, notably those of the hands and feet. It is obvious that if a series of such pictures could be taken from time to time and preserved a most graphic record of progress would be obtained.

The similarity of the changes of the skull in the affection designated hyperostosis cranii or leontiasis ossea and in osteitis deformans has repeatedly been observed, and Paget recognized the importance of discriminating between these affections. In the reported cases of cranial hyperostosis the alterations of the skull have sufficiently been described, but, unfortunately, little mention has been made of the

condition of other bones. This omission was due in part to the preservation of the skull alone, in part to the less striking changes in other portions of the body, perhaps from the early stage of their development, or because attention was not directed to their possible presence.

Within the past ten years renewed attention has been called to cranial hyperostosis, especially through the publications of members of this Association, notably Drs. M. Allen Starr, Putnam, Prince, and Edes.

This disease is usually described as occurring early in life and as almost exclusively concerning the bones of the skull and face. The hyperostosis is frequently combined with sclerosis. The narrowing of foramina, fissures, and cavities, and the deepening of canals are emphasized. Affections of sight and hearing, facial paralysis, difficulty in chewing, swallowing, and breathing are to be found among the disturbances, and the cerebral functions generally suffer.

Nevertheless the difficulty of regarding cranial hyperostosis as an independent disease is repeatedly experienced. Baumgarten, in 1892, discussed the possible relation to Paget's disease, and M. Sternberg (Nothnagel's *Sp. Path. und Therap.*, 1899, vii. 22) admits that some of the cases described as cranial hyperostosis should be regarded as osteitis deformans. Atkinson (*Maryland Medical Journal*, 1901, xliv. 281) considers that the former is a manifestation of the latter. Crozer Griffith at the last meeting of this Association also expressed the opinion that a sharp separation between the two diseases is at present impossible. Cranial hyperostosis has appeared at a late period in life, and osteitis deformans is not limited to advanced years.

The failure to recognize bone lesions elsewhere in cranial hyperostosis is not necessarily due to their absence, and the case here reported by Dr. Prince and myself gives evidence that the bones of the face may be diseased in osteitis deformans. The skull brought to this country by Spurzheim, and now preserved in the Warren Museum of the Harvard Medical School, and usually regarded as an example of cranial hyperostosis, shows the changes described as occurring in Paget's disease, while the skull of the case reported by Putnam as cranial hyperostosis shows extensive sclerosis, little or no rarefaction, and not much enlargement, alterations suggestive rather of syphilis than of Paget's disease. (See Plate V.) The presence of mental

derangement cannot be regarded as of significance in the differential diagnosis, since our patient with Paget's disease eventually so suffered from delusions and loss of self-control as to require treatment in an asylum.

It would seem from the above considerations that hyperostosis is a condition which may affect few or many bones, early or late in life, and with inconstant symptoms; that the evidence in favor of the recognition of an independent disease, diffuse, cranial hyperostosis is insufficient, since the symptoms assigned to this affection are inconstant, and may occur in osteitis deformans.

Finally, of the twelve reported cases which, according to M. Sternberg, serve as the basis of the clinical study of this affection, one at least, as shown by Dr. Prince, eventually proved to be an example of osteitis deformans, while the cranium of another, subsequently obtained by Dr. Putnam, showed lesions suggestive rather of syphilis than resembling those present in the hyperostotic skull from the Spurzheim collection, which correspond to those described by Paget as occurring in osteitis deformans.

OSTEITIS DEFORMANS.

By M. HOWARD FUSSELL, M.D.,
OF PHILADELPHIA.

THOMAS W., aged seventy-eight years. Each of his parents lived to over eighty years. He had eight brothers and sisters, of whom none survive, but they all lived to about the age of the patient. He is married and has had two children, one of whom died at four years; the other, a daughter, is living and well.

When he was fifty years old (twenty-three years ago) he had an attack of pneumonia, and since that time he has never been entirely well, having had repeated attacks of asthma, and in the last ten years a marked dyspnea, with signs of failing heart, due to an emphysema. He has taken large quantities of opium, and at present he is in the mental state resembling senile dementia.

On examination he was badly emaciated, with edema of both legs. He has a complete right inguinal hernia; he has marked abdominal breathing, with a typical barrel-shaped chest. There is hyperresonance over the whole chest; marked prolongation of expiration. The chest expansion is three-fourths of an inch.

The heart dulness is from the right border of the sternum to half an inch inside of nipple line and to the upper border of the third rib. There is a marked systolic murmur in the region of the tricuspid valve. This murmur has existed for the last five years, and is gradually increasing in severity. For the last twenty years his family has noticed that he has gradually become stooped, that his legs have become bowed, and that his head was increasing in size. The point which especially attracted their attention was the enlargement of the head, with marked irregularities over the cranial surface. When stripped and examined with special attention to the bony deformities which exist the following conditions were noted: The head is large, flat on top, with a triangular face. The chin is thrust forward and down on the chest. The spine is curved posteriorly, giving a marked round-shouldered appearance. His legs are very markedly bowed, as seen in the photograph, the greatest bowing being in the femora. His height twenty years ago was 5 feet 10 inches; at present it is 5 feet 5½ inches. There is a marked transverse groove in the upper part of the abdomen.

The fontanelles are all closed.

FIG. 1.

FIG. 2.

FIG. 3.

FIG. 4.

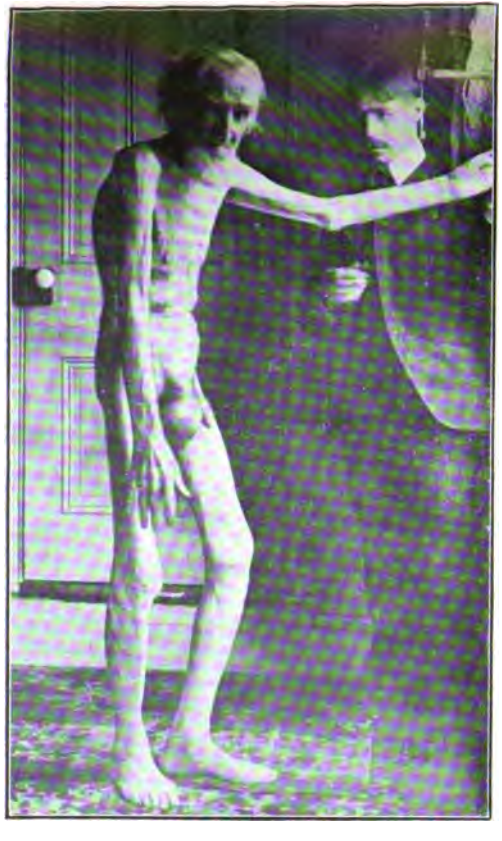
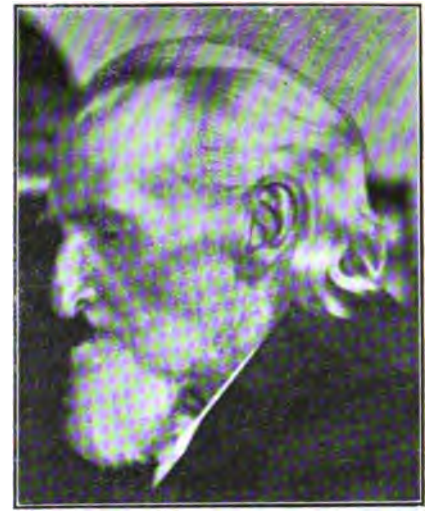


FIG. 5.

Showing broad skull.

FIG. 6.



Showing depression in skull.

OSTEITIS DEFORMANS.

The head is enlarged; both parietal protuberances are remarkably prominent. It is flat on top, and scattered irregularly over the surface of the cranium are marked prominences alternating with depressions. These prominences and depressions are yearly growing more marked, being due, doubtless, to irregular thickening of the vault of the cranium. The circumference of the head is 23½ inches; the distance from meatus to meatus is 12 inches. The distance from the occipital protuberances to the base of the nose is 13½ inches. The bones of the face are not changed, neither is the lower jaw; the lack of enlargement in the face compared with the enlarged skull gives the face an especially small appearance.

Upper Extremities. Clavicles: Both clavicles are very prominent and thickened, the right being much thicker than the left, the greatest amount of thickness being in the middle portion. There is a marked curve backward of the clavicle at this point of thickening.

Scapulæ. The outline of both scapulæ is normal, but the spines of both are markedly increasing in thickness, and the scapula itself is increased in thickness.

Spinal Column. The spinal column is almost immobile; there is marked bowing posteriorly, the greatest amount of bend being in the thoracic region. So great is the bowing and so limited is the motion that it is impossible to touch the head and shoulders at the same time against the upright support for measurement.

Ribs. The ribs are very markedly thickened, measuring about 1½ inches in breadth.

Humeri. Neither of these bones is changed to any extent.

Ulna and Radius. Right: Both of these bones are enlarged, but not markedly bent. *Left:* They both are thickened, the ulna particularly so in its middle portion, and are both bent outward.

Hands. There is no change in the bones of the hands or wrists; there is no involvement of the joints of the upper extremities.

Pelvis. Both ilii are markedly thickened and flattened, giving the pelvis an extremely broad appearance. The distance between the anterior superior spinous process is 12½ inches.

Lower Extremities. Right: The femur is very markedly thickly bowed anteriorly and outwardly; the greatest bowing is in the upper third. About the same condition exists in the left. The lower end of both femurs is thickened.

Tibiæ. Both tibiæ are markedly thickened and bowed anteriorly and outwardly; the fibulæ are also thickened and bowed anteriorly and outwardly. The bones of the ankle and foot are not changed.

As above noted, the lower ends of both femora are thickened, but there is no arthritis, and the movement in the joints is perfect and painless. There is marked muscular wasting, but this can unquestionably be accounted for rather from the standpoint of the general condition of the patient, his long confinement to the house, and his distressing illness (emphysema), which has lasted for so many years.

The patellar reflexes are perfectly normal.
The pupillary reflexes are perfectly normal.
The cremasteric reflex is perfectly normal.

(In view of the excellent papers of Packard, Steele and Kirkbride, and of Dr. Prince, read to-day, the literature and pathology of these rare cases is not discussed.)

A REPORT OF NINETY-TWO CASES OF THERMIC FEVER TREATED AT THE PENNSYLVANIA HOSPITAL IN THE SUMMER OF 1901.

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The 92 cases of thermic fever upon which this report is based occurred in the service of the writers at the Pennsylvania Hospital, Philadelphia, during the extremely hot weather of July, 1901, and includes all those showing a temperature of 100° F. and over, upon admission, and does not include a large number of cases of heat exhaustion. These records, unfortunately, are far from complete, as the extra work thus suddenly thrown upon the hospital staff made it impossible to keep full and accurate notes, the question of treatment being the one of paramount importance. Enough data have been secured to warrant, in our opinion, this report. The amount of work may be appreciated when it is known that 1000 cases of all kinds were admitted into the wards during the first week of July.

Seventy-six cases were admitted on the first three days of July, 1901, with 19, 26, and 31 cases, respectively. These three days followed three very warm days in June, with a maximum temperature varying between 96° F. and 99° F. The maximum and minimum temperatures of these three days in July were as follows:

	Maximum.	*Minimum.*	
July 1 . .	100	82	
" 2 . .	102	94	(These days also showed a high humidity.)
" 3 . .	105½	80	

These records were kept at the Pennsylvania Hospital, and although higher than the official records kept by the Weather Bureau, probably represent more closely the temperature experienced by the great mass of people.

The first case was admitted on June 23d, while from the 6th to the 16th of July no case was admitted owing to a decided fall in the temperature.

The time of day at which the greatest number were received was

from 11 A.M. until 5 P.M., the maximum being from 3 to 5 P.M., toward the close of the working day, showing the effect of fatigue and long exposure.

But little time probably elapsed between the onset of the attack and the admission of the patient into the hospital.

Sex. Thirty-one of the cases treated were females, as against 60 males. This is an unusually large proportion of women, but it should be mentioned that the most severe cases were usually found in men.

Age. The extremes of age of the cases were from seven months to over seventy years, the average being about thirty-seven years. Among the elderly patients might be mentioned one aged seventy years (died, temperature 110⅘° F.), one aged seventy-three years (cured, temperature 108° F.), one aged seventy-five years (cured, temperature 107⅘° F.), and one aged seventy nine years (cured, temperature 108° F.).

Color. Six of the number were negroes, emphasizing the previously well-known immunity of this race.

Nationality. The largest proportion of patients were natives of the United States.

Of the patients showing a temperature of—

100° F.	to	and	not	including	101° F.,	there	were	.	.	.	24	cases.
101	"	"	"	102	"	"	.	.	.	8	"	
102	"	"	"	103	"	"	.	.	.	10	"	
103	"	"	"	104	"	"	.	.	.	4	"	
104	"	"	"	105	"	"	.	.	.	4	"	
105	"	"	"	106	"	"	.	.	.	4	"	
106	"	"	"	107	"	"	.	.	.	8	"	
107	"	"	"	108	"	"	.	.	.	6	"	
108	"	"	"	109	"	"	.	.	.	8	"	
109	"	"	"	110	"	"	.	.	.	2	"	
110	"	"	"	111	"	"	.	.	.	8	"	
111	"	"	"	112	"	"	.	.	.	3	"	
112	"	"	"	113	"	"	.	.	.	1	"	
				"High"	.	.	.	.	.	1	"	
				"Unknown"	.	.	.	.	.	1	"	
										92	"	

No patient with a temperature under 106° F. died, but above this temperature the proportion of "cures" to deaths was as follows:

106° F.	to	107° F.	6	cures	and	2	deaths.[1]	A mortality of 25 per cent.
107	"	108	5	"	"	1	"	" 15.6 "
108	"	109	7	"	"	1	"	" 12.5 "
109	"	110	1	"	"	1	"	" 50 "
110	"	111	5	"	"	3	"	" 37.5 "
111	"	112	0	"	"	3	"	" 100 "
112	"	113	0	"	"	1	"	" 100 "

[1] These cases, which so inordinately raise the percentage mortality for this class, are detailed somewhat below.

No case with a temperature of 111° F., or over, recovered.

The total number of deaths numbered 13, a mortality of 14 4 per cent. The case recorded as of "unknown" temperature died, and is not included in the above percentage of deaths.

Convulsions. These were noted in 14 cases and were generally of severe type. They were largely tonic in character, and did not resemble those seen in epilepsy or in uremia, and usually occurred in those showing a temperature of 106° F. or over. Retraction of the head was seen in several cases, with or without convulsions, and some showed marked excitement after the temperature was reduced, and struggled violently.

Five of the cases were not convulsed on admission, but showed this symptom after the temperature was reduced by rubbing with ice, with or without bleeding and transfusion. These cases will be spoken of again under the heading "Treatment." Some of the convulsions were unusually severe and tetanic in character. In one case where the temperature only reached 101⅘° F. there were marked tonic spasms of the hands and feet after consciousness was regained.

Mental State. Patients showing a temperature of 106° F., and over, were generally unconscious when brought to the hospital, although one case was unconscious with a temperature of only 101⅘° F., while the term "semiconscious" was recorded for many having the lower grades of temperature. Marked cerebral excitement, even requiring restraint, was seen n a few cases after the reduction of temperature was accomplished.

Pupils. Careful records of the state of the pupils were not kept. In 5 cases the pupils were noted as "contracted" in patients whose temperatures varied from 104⅕° F. to 111⅗° F. In 2 cases with a temperature of 110° F. the pupils were noted as "dilated." Nystagmus, both horizontal and vertical, was noted in 1 case with a temperature of 108° F.

Knee-jerks. The condition of the knee-jerks was examined in 6 cases where the temperatures varied from 101⅘° F. to 110⅘° F. These patients were all unconscious when admitted, and had either retraction of the head or convulsions, which were either tonic and local, or clonic and general. The patient whose temperature was 101⅘° F. was unconscious on admission, but upon a return to consciousness after treatment had tonic contractions of the hands and feet, and showed a marked increase in the knee-jerks, as might be expected from the reinforcement. The remainder of the cases had a total absence of knee-jerks. It is not noted at what time of the patient's stay in the hospital this symptom was noticed, except in 1 case. In this case the temperature reached

110° F., the man was profoundly unconscious and had dilated pupils, there was also retraction of the head, but at no time were there any true convulsions. He rapidly responded to the ice-rub and did so well that no other treatment was instituted. His knee-jerks were entirely absent on the day of his discharge, three days after his admission. An examination recently made of this patient showed the knee-jerks to be present, although a little less pronounced than usual. A second patient whose temperature also reached 110° F., and in whom this absence was noted, has upon a recent examination shown a return of this reflex. This case had violent convulsions after his temperature had been reduced by treatment.

A third case, that of a powerful negro, was admitted totally unconscious, with a temperature of 108° F. This man also had general tetanic convulsions coming on after the reduction of temperature following the use of ice, bleeding, and transfusion. On the first day of his stay in the hospital it was found that he had absent knee-jerks. On recent examination of this patient, who still claims to be as powerful as ever, it was found that only the slightest possible knee-jerk could be obtained by reinforcement. His station was good, and he had no other evidence of disease of the spinal cord that could be detected.

It is worthy of note that two of these patients state that since the thermic fever they have been impotent, although before their attack they had been possessed of full vigor.

Urine. The urine was examined in 10 cases, but usually not until convalescence had set in, or the case had been retained in the hospital for several days. In 4 of these cases, with temperatures of 100⅘° F., 107° F., 110° F., and 110⅘° F., albumin in varying amount, with granular casts, was found. In 1 case granular casts, without albumin and in another albumin in small amount without casts were found. The urine record of the case showing a temperature of 110° F., an occasional hard drinker, aged forty-eight years, was as follows: specific gravity 1019, acid, albumin, no sugar, dark granular casts containing blood. This case was lost sight of until very recently, when an examination of the urine gave the following results: specific gravity 1015, distinctly alkaline, light yellow, cloudy, albumin and sugar negative, triple phosphates, calcium phosphates and amorphous phosphates, making it probable that the thermic fever and not the previous physical condition had been the cause of the renal disturbance. In 2 cases sugar was found, 1 having a temperature of 102⅕° F., which was probably a true case of diabetes mellitus; in the second, with a temperature of 108° F., the "sugar" disappeared a few days after its discovery.

Habits. The previous habits of the patient seemed to have an important bearing upon the result, and to affect the latter unfavorably. In the mild cases no alcoholic history was obtained, possibly from lack of interest in the case or from press of more important work, and all recovered. In the severe cases 50 per cent. of those recovering gave an alcoholic history, and of those who died the same percentage was found. This record as to the use of alcohol was not made in all of the severe cases.

Blood. It was thought that many if not all of the symptoms of thermic fever might be due to dehydration of the blood from prolonged and excessive sweating. According to Vincent (Bordeaux *Thesis*, 1887) Chossat in 1868 first broached the theory that thermic fever was due to excessive sweating and loss of water by evaporation from the lungs. A considerable number of experiments have been performed upon animals to show the effect of exposure to heat upon the composition of the blood. A few of these may be worthy of citing.

Vincent, in experimenting on animals, found an increase in the hemoglobin percentage and an augmentation of the number of red cells by 300,000 per cubic millimeter.

Grawitz (*Zeitsch. f. klin. Med* , 1892, Bd. xxi. p. 465), also by animal experimentation, found the specific gravity of the blood usually progressively increased by sweating, although in a small number of cases there was a lowering of the specific gravity. In 1 case the specific gravity rose from 1040 to 1051.

Löwy (*Berl. klin. Woch.*, 1896, No. 41) exposed rabbits to heat for twenty-four hours and found a diminution of the thickness of the blood and dry residue, but all of the tissues "poor in water." The blood serum, on the other hand, was found to contain less water than normal, and while the specific gravity of the blood was found to be diminished, that of the serum was decidedly increased. He attributes these alterations to changes in the vascular tonicity.

Friedländer (*Fortsch. der Med.*, July, 1897, p. 521), also by experimentation, found an increase in the number of the erythrocytes, still more marked increase in the number of the leukocytes, and an increase of the specific gravity and of the thickness of the serum.

Scagliosi (*Virchow's Arch.*, 1901, Bd. clxv., pp. 15 to 41) placed guinea-pigs in the sun in August and September and found an increase in both the erythrocytes and the leukocytes, especially the latter. He concludes from his experiments that "the blood shows an excessive increase in thickness of all formed elements, and of the neutrophilic cells. In some cases, also, a leukocytosis was present."

We can find but little evidence as to the condition of the blood in human beings exposed to excessive temperatures. Alexander Lambert (Loomis-Thompson, *Amer. Syst. of Practical Med.*, 1898, vol. iii. p. 873) states that in 1896 the hemoglobin value in 12 cases examined ranged from 85 per cent. to 125 per cent. Leukocytosis was present and the leukocytes contained pigment. The changes described were present in those whose temperatures did not reach 105° F., as well as in those with higher temperatures.

Owing to the small amount of exact knowledge as to the condition of the blood in human victims, and owing to our thought that in changes in the blood an explanation of at least some of the symptoms might be found, it was our intention to pay particular attention to the condition of the blood in any cases of thermic fever brought to the hospital during the past summer. Unfortunately, the hot days caught us unprepared for as complete investigations as we should have wished. The blood was examined in 17 cases. Among these, curious irregularities were found, making it impossible at present to do more than summarize them. In bleeding patients with sunstroke the dark color of the blood, not resembling ordinary venous blood, was noted. We had, therefore, hoped to obtain some facts regarding spectroscopic changes. Owing to the impossibility of at once obtaining the necessary apparatus a spectroscopic examination was made in only 2 cases, and in both of these the absorption band of hemoglobin was found alone, although the appearance of the blood led us to think that possibly methemoglobin might be present. The specific gravity was estimated in 4 cases; in 3 the specific gravity was 1055, 1056, and 1057, respectively. The fourth showed a specific gravity of 1074. This latter blood was from a patient who died two hours after admission in spite of everything that could be done for her. In this same patient the hemoglobin value was 83 per cent., and the erythrocytes numbered 5,040,000, it being the only case in the series in which the erythrocytes were increased. The hemoglobin was estimated in 5 other cases and amounted in these to 67, 85, 68, 74, and 68 per cent. The absence of constant high specific gravity and of increase in the number of the red cells rather surprised us, as we expected to confirm some of the results reported by others in this direction. The number of the leukocytes varied greatly. All but 3 of the severe cases examined showed at some time a high leukocyte count, but there was considerable irregularity in the time and duration of the rise. In some cases a leukocytosis of from 12,000 to 13,000 was noticed on admission. The increase was usually in the polymorphonuclears. In most of the cases in which there was a primary

rise in the number of leukocytes followed by a fall and then a second increase in number, delirium tremens developed. No experiments regarding the toxicity of the serum for animals were made.

These results surprised us, especially as at the time when they were being obtained in the Ayer Laboratory of the hospital we felt justified in believing that the injection of large quantities of normal salt solution was saving some lives. To this view we still adhere.

It is a well-known fact that the treatment employed in thermic fever, viz.: cold baths, hypodermoclysis, transfusion, and bleeding, can alter materially the normal proportion of the elements of the blood.

In our cases, unfortunately, the examinations of the blood were made without any definite relation in time to the treatment as mentioned above, which might alter the findings, and in consequence vitiate somewhat the conclusions drawn, and explain in some degree the apparent discrepancies. Two explanations of the apparent contradiction of the clinical and laboratory results in our cases present themselves. It seems to us conceivable that the absence of marked elevation of the specific gravity of the blood, of its hemoglobin contents, and of the number of the erythrocytes may be due to the rapid passage of water from the tissues to the blood, as is seen in Hay's treatment of pleurisy with effusion, in removal of anasarca by eliminating methods, and in cholera. This theory it would be difficult to prove. A very plausible explanation of the benefit of the treatment used is that made practically certain by the work of Levene and Van Gieson as to the increased toxicity of the blood. Lambert (*Medical News*, July 24, 1897), who quotes these authors, also found that serum from the blood of some thermic fever patients caused the death of rabbits in doses of .9 c.cm. within an hour.

The serum removed at once was found by him to be less toxic to animals than was the serum of the same patients twenty to forty-four hours later.

If this autointoxication be the true explanation of the phenomena of thermic fever, the beneficial effects of hypodermoclysis or intravenous injection of saline solution can be readily explained by the "washing of the blood."

Treatment. The treatment of the mild cases (100° to 102° F.) can be dismissed with a few words. In this class there were 32 cases, although there are not included a large number of patients, the notes of whose condition are insufficient to allow of their classification. The indications for treatment in this class of cases were simply rest in a cool portion of the ward, the application of an ice-cap, the administra-

tion of the aromatic spirit of ammonia, or alcohol, or strychnin, and occasionally a cool bath. The cases whose temperature ranged from 102° to 106° F. numbered 22. These showed more severe symptoms than the milder group, and an approach to the symptoms of the higher temperatures was occasionally noted. The treatment of this class consisted in the administration of stimulants, as they were required by the state of the pulse, the application of an ice-cap, and either a cold bath or, in the more obstinate cases, the employment of rubbing with ice until the temperature approached the normal. None of these cases died. Cases with a temperature between 106° and 108° F. numbered 14. Three of these died, one being a man with a temperature of 107⅘° F., the second a man whose temperature was 106° F. on admission, and who later died with well-marked typhoid fever, and the third being a woman in whom alcohol undoubtedly played a more prominent part in causing death than did the result of heat. These cases were taken to the heat tent, where they were treated in the manner mentioned below in considering the cases of still more severe type, where the temperature was 108° F., or over. The cases whose temperature reached a point equalling or surpassing 108° F. numbered 22. Of these 9 died. One case of "unknown" temperature died; 1 case with "high" temperature recovered.

All of the cases except those with a temperature below 102° F. were treated in a large tent open at the ends, covered with a fly and having an asphalt graded floor. The fly was kept constantly moist by means of a lawn-sprinkler placed on the ridge-pole, an expedient that did good service and did not seem to increase the humidity. Within the tent there were two large electric fans constantly working, and faucets were conveniently arranged for the furnishing of cold water. The tent was furnished—aside from the beds—with a movable bath-tub and a medicine cabinet. In a few cases the hose was employed by directing a stream of water from a distance over the patient's body. The experience this summer in the few cases in which this method was employed rather tended to confirm the observation of former years. While this method of applying cold seemed to aid respiration it rather increased the tendency to convulsive movements. The use of the bath-tub was soon abandoned, owing to the impossibility of reducing the temperature by this means with sufficient rapidity to at all keep pace with the number of admissions. In addition to this, it required more physical labor to lift the patient in and out of the tub, and to practice friction on the surface than was the case with rubbing with large pieces of ice, which acted more rapidly and equally beneficially in reducing the tem-

perature. In many cases the temperature fell rapidly to normal after rubbing with ice from ten to fifteen minutes. With the fall of temperature consciousness frequently returned, and the patient required no further attention. Frequently with the return of consciousness delirium occurred, which was at times quite violent, and in a few cases persisted for some hours. Exceptionally a second rise of temperature occurred, but seldom to such a height that it was not controlled perfectly by either a cold sponge or one cold bath.

The question as to the advisability of bleeding in cases of sunstroke has been much discussed. As a routine measure of treatment we would by *no means* advise it. In certain cases, however, where with the fall in temperature there was not a corresponding decrease in the other grave symptoms, as well as during the existence of high temperature in desperately ill cases, we found it beneficial. Feebleness of the pulse was not considered a contraindication to this procedure, and in some cases the character of the pulse improved as the blood flowed from the arm. The measure was employed in 8 cases. Of these 4 died. In regard to bleeding, as well as in regard to the two measures still to be noticed, it is to be remembered that it was only employed in the most severe cases. The mortality percentage among cases in which venesection was practised was, therefore, necessarily high. It is our belief that in no case did the removal of blood do any harm, and in many cases the abstraction of blood was followed by an improvement in the circulation, in the character of the breathing, in the color of the patient, and in the mental state, due either to this or to the introduction of saline solution. The amount withdrawn varied from 6 to 20 ounces.

The employment of normal saline solution introduced by various channels was first advocated upon purely theoretical grounds. As has been said above, while there is some evidence that diminished serosity is present in some cases, none of the tests which we were able to employ to confirm the existence of this condition enabled us to assert its presence in our cases. This will be seen in the detailed report of certain cases, with the account of the blood picture in the cases wherein this was examined. Hypodermoclysis was employed in 5 cases. All of these were of the severest type. Of this number 1 died. It was found that this method of introducing salt solution occupied too much time to be perfectly satisfactory. We believe that valuable time may be lost in getting the saline solution into the circulation by this measure, and it has the additional disadvantage of requiring the undivided attention of at least one person during ten or fifteen minutes at a time when rapid work is essential even with a large staff of assistants. Intravenous

injection of normal saline solution was found to be more applicable because of the greater rapidity with which the blood was affected, and also because of the saving of time on the part of the assistants. This measure was employed in 10 cases; of these 4 died. The operation was readily performed and took but little time, because in the large majority of cases the same incision in the median basilic vein employed for bleeding was at once used for the injection of the saline solution. Although the conditions were by no means favorable for thorough antisepsis, in spite of all efforts to accomplish this, it is to be noted that in no case did any untoward results follow from infection of the wounds made either by the lancet or by the needle.

Our conclusions in regard to the value of the last three measures are that in some cases where the other symptoms do not improve, as the temperature is reduced by rubbing with ice, the abstraction of blood from the median basilic vein to the extent of from 10 to 18 ounces causes the pulse, respiration, and color of the skin to improve. On four occasions convulsions occurred after bleeding and transfusion. While it is difficult to estimate the value of the introduction of normal saline solution, we see no evidence of its having any harmful action, and usually felt assured that the patient's condition was improved by one or the other of these procedures.

Among the sequelæ should be noted 1 case of jaundice coming on three days after onset in a case having a temperature of 110⅘° F., where there was also delirium tremens.

While from the rapidity with which these patients were brought to the hospital we were unable to make as close a study of them and to keep as careful records of their condition as we wished, we make this report in the hope that in the future we may be able to more completely study some of the many points of interest in this condition. It seems to us that valuable results might follow the further study of the condition of the eye-grounds, the specific gravity of the blood, its spectroscopic examination, a frequent estimation of the leukocytes, and a more complete study of the toxicity of the blood serum. We also believe that the introduction of normal saline solution in large quantities into the body has a beneficial result, although the few examinations of the blood which we have had made do not directly point to the method by which it causes relief to symptoms. Possibly the toxicity of the blood, a subject into which we could not enter, may explain its supposed beneficial effect.

Abstracts of Certain of the Cases.

Two of the oldest patients were aged, respectively, seventy-three and seventy-nine years, each of them being admitted with a temperature of 108° F. The oldest of these showed a rapid drop in temperature with improvement in all of his symptoms under rubbing with ice. The younger one, aged seventy-three years, did not recover so completely on rubbing, and was given a pint and a half of normal salt solution under each breast, with rapid improvement of all his symptoms. In the older man, aged seventy-nine years, the temperature did not reach the normal point until four days after admission. Another patient, aged seventy-five years, was admitted with a temperature of 107⅘° F. and rapidly improved under treatment. He has since responded to our inquiry regarding his health at present, that he is weak and unable to walk—possibly as much from the effect of years as from the effect of heat.

Case 1025 should be included in the list of sunstroke occurring in old people. He was a man, aged seventy years, with a temperature of 110⅘° F. on admission, and with all the signs of senile degeneration well marked. Notwithstanding the vigorous application of cold his temperature remained high, rising to 108° F. after the primary fall to about 103° F. He died on the fourth day with a continued high temperature. He was neither bled nor transfused.

Case 1258.—P. M., male, aged forty-one years; brought in with a temperature of 110⅘° F. He was bled 12 fluidounces, and transfused 1 quart. His temperature fell to 101⅘° F. in about four hours, and he regained consciousness. The next day all he complained of was a slight headache. His knee-jerks were absent. He was discharged the next day feeling perfectly well. On the day of admission, hour not mentioned, his leukocyte count was 7500, and when discharged the count was also 7500.

Case 1138.—W. W., male, aged thirty-eight years; a moderate drinker of beer and ale, was admitted with a temperature of 106⅘° F., conscious, and with a diffused red rash over the body; he was given an ice-rub, and in two hours his temperature had fallen to normal, and with the exception of a headache he felt well. He was discharged the next day. His blood examination on admission showed leukocytes, 9200, and on the following day 9850.

Case 914.—H. C., male, aged fifty-two years; admitted June 23, 1901, with a temperature of 104° F., conscious, although somewhat

stupid and with severe headache and backache. His pupils were equal and contracted. He was given ice-rubbing and bathing. His temperature did not fall until the eleventh day, having been kept up by an intercurrent attack of enteritis. A leukocyte count taken on the day of admission, immediately after the ice-rub, gave 16,000. On the following day the specific gravity of his blood was 1055, the hemoglobin 68 per cent., and the erythrocytes 4,906,000.

Case 1025.—J. W., male, aged seventy years; brought into the hospital in an unconscious condition, with a temperature of 110⅘° F., pulse feeble, pupils contracted, face cyanosed, head retracted. He was given an ice-rub, which was continued for over an hour, by which time the temperature had fallen to 102° F., and he became partially conscious, although unable to speak or understand. His arteries were very atheromatous, and arcus senilis was present. History of the previous free use of alcohol was not obtained. Knee-jerks were entirely absent. The urine was acid, with specific gravity of 1019. There was a ring of albumin, but no sugar. A few granular casts were found. After admission to the wards his temperature rapidly rose again, and on the fourth day he died despite the application of ice and the use of strychnin and nitroglycerin. The thermic fever in this case was merely the last chapter in a case of an old man with general arteriosclerosis. Before the ice-rub his blood was examined with the following result: specific gravity, 1056; erythrocytes, 4,225,000; leukocytes, 13,500; hemoglobin, 85 per cent.

On July 2d, the next day, 10.30 A.M., hemoglobin, 75 per cent.; leukocytes, 9850.

On July 3d, time not given: leukocytes, 11,000. Differential count: polymorphonuclears, 94.8 per cent.; small mononuclears, 48 per cent.; large mononuclears, 4 per cent.; eosinophiles, none.

Case 1044.—L. R., female, aged twenty-seven years; brought into the hospital unconscious, and with a temperature of 110° F. Her temperature fell to 105° F. under ice rubbing in three-quarters of an hour; she then had two convulsions, which were relieved by one-quarter of a grain of morphin hypodermically. Later in the day she was transfused with normal salt solution. For hours she was in constant tetanic spasm, and at times was quite noisy. Her temperature subsequently remained above 105° F. She had constant ice-rubbing, with no avail. She died twelve hours after admission.

Case 1126.—C. Z., male, aged thirty-nine years; was brought into the hospital with a temperature of 110° F., unconscious and pulseless, with cyanosed face, contracted pupils, and retracted head. He was

rubbed with ice, and bled 11 fluidounces, and then transfused with one and one-half quarts of normal salt solution. Strychnin and digitalis were given hypodermically, and one pint of cold water enteroclysis given. When his temperature fell to 105° F. he went into violent convulsions. Two hours after admission his temperature had fallen to 102⅘° F., and he regained consciousness, but by evening his temperature had risen to 106° F., and he was again unconscious. The next day consciousness returned and he developed delirium tremens, and it was then learned from his friends that he was seldom sober. On the third day his temperature rose to 106° F., and he died with signs of pulmonary edema. On the day of his death, the third day after admission, his blood gave the spectrum of dilute hemoglobin only.

Case 1130.—J. B., male, aged forty-nine years; was brought in unconscious with a temperature of 110° F., with rapid pulse, widely dilated pupils, and retraction of the head. This patient responded so rapidly to the ice rub that neither hypodermoclysis nor transfusion was resorted to, the temperature falling to normal in three hours. His knee-jerks were absent.

Case 1129.—S. R., male, aged sixty-three years; was admitted unconscious, with a temperature of 106° F. and pulse 132; he had incontinence of feces, and was very restless and noisy. He was given an ice-water tub, but the temperature only fell one degree, when a profuse rash appeared. After an ice-rub the temperature fell to 102⅘° F., and two hours after admission it was nearly normal. The man subsequently developed delirium tremens. His urine contained no albumin, but did contain a few granular casts. On the fifth day his leukocytes were 12,125. He made a perfect recovery, and was discharged on the twelfth day.

Case 1141.—W. J., male, aged fifty-seven years; a heavy drinker, was brought in with a temperature of 109⅘° F., profoundly unconscious, with strong odor of alcohol on his breath. He was rubbed with ice, and bled 10 fluidounces and transfused one quart of normal salt solution. A hypodermic injection of strychnin ($\frac{1}{30}$ grain) was given. In three hours the temperature fell to 99¼° F., he then went into severe convulsions, which were quieted by a hypodermic injection of ¼ grain of morphin. On the third day his temperature began to rise, and he went into delirium tremens, and after developing Cheyne-Stokes respiration died on the following day. The leukocyte count was made immediately after admission, during transfusion, and showed 13,200. On July 4th, the day after admission, the count was 9200, and on the 5th, while in delirium tremens, the leukocyte count was 14,650. His blood gave the spectrum for hemoglobin only.

Case 1161.—S. B., male, aged forty-one years, colored; brought in unconscious with a temperature of 108° F. An extremely muscular man, weighing 195 pounds. He was given an ice-pack, was bled 8 fluidounces, and transfused one quart. In less than two hours his temperature had fallen to 99° F., he then went into severe tetanic convulsions, for which morphin was given. By evening he regained consciousness, and felt none the worse for his experience. His knee-jerks were absent. He was discharged feeling well in two days. When seen ten months later his only complaint was an absence of sexual power.

Case 1142.—M. K., male, aged fifty-three years; was admitted at 2.15 P.M. on July 3d, with a temperature of 108° F. He was not unconscious, but was very weak, his pulse being not perceptible, but after the administration of ammonia it became so, and was 140 per minute. Under the ice-rub his temperature rapidly fell and became normal in less than two hours. He was discharged the next day apparently well. His leukocyte count before the ice-rub was 12,160, but by the next day it had fallen to 8700.

Case 1014.—L. N., female, aged twenty-one years, was a large healthy-looking woman; she was conscious when admitted, and with a temperature of 107° F. She had been ailing for some days before admission, and had had a convulsive seizure of some kind on the night before. She was rubbed with ice and given ammonia, but her temperature did not fall to normal until the next morning. She was discharged well on the third day. Before the ice-rub the specific gravity of her blood was 1057. The other blood examination was made after the ice-rubbing, and was as follows: Hemoglobin, 65 per cent.; erythrocytes, 4,166,000; leukocytes, 10,250. On the next day the leukocytes were 7350, and on the day of discharge 8860.

Case 1027.—E. G., male, aged forty-eight years, tailor. Patient was overcome in his shop and was brought into the hospital in an unconscious condition, having but recently recovered from a debauch. His pulse was rapid, hard, and tense, his temperature was 110° F., his face cyanosed, his body rather rigid, and his head retracted. Patient had involuntary fecal movements. He was rubbed with ice, but as the temperature did not seem to fall quickly under the icing, a vein was opened in the arm and the patient was bled 6 fluidounces. Two quarts of normal salt solution were given into the opened vein, and in about one-half an hour his temperature fell to 104⅕° F. He then went into a general convulsion, which, however, affected the hands especially. Five hours after admission the patient was still unconscious, with stertorous respira-

tion, but with a better pulse. Under further treatment with ice his temperature fell to 102° F., but by evening, after admission into the ward, it rose to 105° F.; tub-bathing was resorted to, but it was not until next morning that he regained consciousness. The urine then showed: specific gravity, 1019; ring of albumin, no sugar, dark granular casts containing blood. His knee-jerks were entirely absent. There was no paralysis. He remained in the hospital eleven days, and was discharged well but weak. When seen ten months later he expressed himself as feeling perfectly well, with the exception of an entire loss of sexual power, a condition which had not existed before. His urine was normal. Immediately after the ice-rub his blood was examined and showed: hemoglobin, 67 per cent.; erythrocytes, 4,352,000; leukocytes, 8500. The leukocyte counts in this case subsequently were as follows: July 2d, 12.30 P.M., 10,466; 3d, 10.30 A.M., 10,250; 5th, 6 P.M., 8160; 8th, 10 A.M., 6000.

Case 1039.—E. G., female, aged fifty-eight years; brought into hospital unconscious with a temperature of 108° F., with a full, strong pulse, and cyanosed face. A vein was opened in the arm, but before anything else could be done she died, fifteen minutes after admission.

Case 1033.—Aged seventy-nine years, was admitted with a temperature of 108° F., and recovered promptly under treatment. Twelve minutes after admission the leukocytes were counted and found to number 11,750; polymorphonuclears, 72.4 per cent.; small mononuclears, 23.2 per cent.; large mononuclears, 4.4 per cent. On the day after admission, without evident reason, the leukocytes numbered 15,000. On the third day after admission they numbered 6000; on the day of discharge, six days after admission, they were 8000.

Case 1038.—Was admitted at 4 P.M., on July 2d, with a temperature of 110⅘° F. On admission the leukocytes numbered 14,800; on July 3d, 11,320; on July 5th, 7850. He was discharged cured July 5th.

Case 1123.—Aged seventy-three years, was admitted on July 2d, with a temperature of 108° F. Beside rubbing with ice he was given one and one-half pints of normal saline solution under the skin. On the day of admission the leukocytes numbered 8525. July 3d, without evident cause, they numbered 9730, on July 5th, 13,800. He was discharged cured on the latter date.

Case 1034 was almost moribund when he was admitted at 2.30 P.M. on the afternoon of July 2d. Unconsciousness was complete; respirations were shallow and almost imperceptible, the pulse could not be felt at the wrist, the face was cyanosed, and there was present the curious mixed tonic and clonic convulsion so characteristic of thermic fever.

The temperature in the rectum was 112° F. For a few minutes artificial respiration was practised, and free stimulation was instituted from the beginning. After a few minutes of artificial respiration oxygen was employed with benefit, while the patient was being rubbed with ice. By means of ice the temperature was shortly reduced to 104⅘° F., but as the patient's cyanosis, complete unconsciousness, and extremely feeble cardiac action with shallow respirations continued, he was bled to the extent of 16 ounces. Bleeding improved the character of the pulse, but the other symptoms still remained in evidence. A pint of saline solution was introduced under the skin and another pint was injected into the median basilic vein. The respirations became deeper and the pulse stronger, while the temperature fell to 100⅘° F. It was hoped that he would recover in spite of the fact that the convulsive movements continued after the above measures had been adopted, but at 8.30 P.M. on the same evening the patient suddenly died, his temperature having again risen to 105⅕° F. not long before death.

Case 1037.—An Italian, aged thirty-five years, was in a dangerous condition when admitted to the heat tent at 3 P.M. on July 2d. His temperature on admission was 109⅘° F. He was completely unconscious, strongly convulsed, with cyanotic face, and passing involuntarily the characteristic yellowish liquid stools. Rubbing with ice soon brought the temperature down to 103⅘° F., but unconsciousness and convulsions and cyanosis continuing, ten ounces of blood were withdrawn from the arm, a pint of saline solution was introduced into the cut vein, and one and one-half pints were given by hypodermoclysis. The notes state that before treatment the pulse was imperceptible and the respirations had almost ceased. After the bleeding and salt solution injections the condition steadily improved, and at 6.30 P.M. the patient was conscious, sat up in bed and asked for a drink of water. In this case the temperature did not reach the absolute normal until four days after his admission, although there was no evidence of any reason for its continued elevation. Before being given his ice-bath the blood was examined as regards the number of leukocytes. They were found to number 8000; polymorphonuclears, 89.2 per cent.; small mononuclears, 9.6 per cent.; large mononuclears, 1.2 per cent. On the next day the leukocytes numbered 13,225. On July 5th (two days after the last count) they numbered 6350. Spectroscopic examination showed only the absorption band of hemoglobin.

Case 1047.—This case showed several interesting features. When admitted, at 4 P.M. on July 2d, he was unconscious, with stertorous breathing, cyanosis of the face, clonic convulsions, and a temperature

of 110⅘° F. He was vigorously rubbed with ice, and during this proceeding struggled violently, although still entirely unconscious. The rubbing quite rapidly reduced the temperature, but the other chief symptoms still continued, and twenty ounces of blood were removed from the median basilic vein, followed by the injection of a pint of normal saline solution, and the injection beneath each pectoral region of one pint of the same material. After the primary fall his temperature rose again to 106⅕° F., between 7 and 8 o'clock in the evening, but speedily fell on a repetition of the rubbing with ice. On the next day he was perfectly rational and conscious, but showed marked icterus of the skin and conjunctiva. Four days after admission a typical attack of delirium tremens began and continued for three days. In spite of the deep pigmentation of the skin no bile was present in the urine. At no time could enlargement of the liver or gall-bladder be detected, and there was no evidence of pain, although this feature might have been concealed by his delirium. The jaundice persisted until his discharge, in apparently perfect health, on July 15th, thirteen days after admission. His temperature was irregular until July 12th, when it remained at about the normal point. On the day of development of the delirium tremens his leukocytes numbered 7500. Two days later the number rose to 9640.

Case 1190.—This case, dying with a temperature of 106° F., cannot be wholly attributed to thermic fever. While it cannot be denied that many of her symptoms and probably the exact time of her death were determined by the effect of heat, she died as does a case of alcoholism, not at all as does one of thermic fever. Death, therefore, should not be attributed to the latter cause.

Case 1007 was a large, fat Italian, admitted with a temperature of 108° F. He was semiconscious and delirious. The pupils were dilated, and there was combined horizontal and vertical nystagmus. In spite of his high temperature his pulse had a fair volume, which was very unusual in cases reaching that degree of severity. After a bath in iced water and being rubbed with ice, there was noticed what has been frequently seen in these cases, a profuse papulo-vesicular eruption of a dull-red color over the chest and abdomen. The temperature fell to 103⅕° F. after treatment for half an hour, and at the same time the delirium was replaced by perfect consciousness and a rational state of mind. The urine examined on the day after admission showed a trace of albumin with a few hyaline and granular casts. The notes state that the reaction for sugar was present, but no statement is made in regard to the test employed. In this case the temperature did not reach normal until one week after admission, although there were no new

signs or symptoms explaining this continuous elevation. On the day before his discharge, one week after his admission, the albumin was still present (0.3 per cent.), but no sugar was found. Immediately after his first bath the blood was examined and showed: erythrocytes, 4,720,000; leukocytes, 16,000; hemoglobin, 75 per cent. Nine hours later (June 30th): erythrocytes, 4,700,000; leukocytes, 9000; hemoglobin, 74 per cent. Next day (July 1st): hemoglobin, 73 per cent.; leukocytes before ice-sponge, 9800; leukocytes after ice-sponge, 7228. July 2d: leukocytes, 9600; 3d, 7250; 5th, 8300.

Case 1013.—A woman, aged thirty-six years, had her blood examined ten minutes after her first iced bath. The specific gravity was 1074; hemoglobin, 83 per cent.; erythrocytes, 5,040,000; leukocytes, 12,500. Death occurred about two hours after the above count was made.

Case 1022.—A baby, aged thirteen months, was admitted with a temperature of 107⅘° F. It died before anything could be done for it, five minutes after admission. From the notes it is not possible to say definitely whether or not this was a case of intestinal intoxication.

Case 1023.—Admitted with a temperature of 111° F., died within eleven minutes of his admission to the hospital before any energetic treatment could be adopted.

Case 1024.—Admitted with a temperature of 111⅘° F., died within half an hour of admission, never recovering consciousness.

Case 1048.—Was dying when admitted, with a temperature of 111° F. Death actually occurred two minutes after admission to the hospital.

DISCUSSION.

DR. BILLINGS: In the great heat which occurred in Chicago in 1891 we had a similar experience to that mentioned by writers of the paper. During the occurrence of convulsions in two cases there were seminal emissions. In one patient who was found unconscious on the street the temperature could not be measured by an ordinary thermometer (as the mercury ascended to the top of the tube). After the usual cold bath he was placed in blankets when his temperature had reached 100°, but the temperature continued to fall, and the patient was collapsed. After applying artificial heat about him his temperature again rose to 110°, and it was necessary to repeat the bath. He recovered ultimately, but both cornea sloughed, and this was thought to be due to the fact that when unconscious the patient lay upon the street with his face upturned to the burning sun, with the result that the cornea became dry and shrivelled.

DR. MUSSER: During the summer of 1901 there were admitted to the wards of the Presbyterian Hospital six cases of true thermic fever—that is, with hyperpyrexia. All of these were treated by phlebotomy and intravenous or hypodermic injections of normal salt solution.

CASE I.—H. Z., aged twenty-six years, white, baker; overcome, while at work at night in his bakery, at a temperature of 115°. Admitted July 23, 1901, 12 midnight. Temperature, 108.4°; pulse, 112; respiration, 40; wildly delirious. Treatment: Tubbed; bled twelve ounces, and given 1000 c.c. normal salt solution, hypodermically, within an hour. Temperature fell to 101°; pulse to 84, softer and regular; respiration to 32, and patient became rational. Lungs clear. Developed phlebitis of left arm, but with this exception made an uninterrupted recovery. Urine negative.

CASE II.—E. S., male, physician, aged sixty years; admitted 12.30 P.M. July 2, 1901. Temperature, 109°; urine negative; pulse, 120; respiration, 20. Treatment: Bled six ounces; intravenous injection of 300 c.c. normal salt solution; tubbed. In two hours' time temperature dropped to 102°, but pulse remained light; temperature remained at 101°. Patient did not regain consciousness, and died on the third day.

CASE III.—B. R., male, brakeman, white; admitted July 2, 1902, 2.05 P.M., very cyanosed. Respiration stertorous, 60 to minute; temperature, 110°; pulse running 170 to minute. Treatment: Ice tub; 1000 normal salt solution hypodermically. Temperature fell to 105°; respiration to 48; pulse not much affected. Did not rally to any appreciable extent, and died at 6.45 P.M., with temperature still at 105° to 106°. Two hypodermics of nitroglycerin were given.

CASE IV.—J. F., male, aged forty-three years, occupation flagman on railroad; admitted July 3, 1901, late in afternoon, unconscious and very cyanotic. Temperature, 110°; pulse, 164; respiration, 44. Treatment: Ice tub thirty-five minutes; bled four ounces and given 1500 c.c. normal solution hypodermically, and nitroglycerin hypodermically. Temperature fell to 105°, pulse to 134, respiration to 34. *Was given oxygen continuously*, but died during the night without material change in condition.

CASE V.—W. M., male, aged fifty-five years, white, motor conductor; admitted July 3, 1901, 4 P.M. Temperature, 110°; pulse, 168; respiration, 44; unconscious, and vomiting continuously; respiration stertorous. Treatment: Tub; bled fourteen ounces; intravenous injection of 500 c.c. normal salt solution while in tub; fifteen minutes later 500 c.c. hypodermically; fifteen minutes later 500 c.c. additional; at 8 P.M., three hours later, 1200 c.c.; in all, 2700 c.c.; hypodermics of nitroglycerin. Never rallied, and died at 1 A.M.

CASE VI.—P. D., aged sixty-five years, white, hostler; admitted July 2, 1901, 4 P.M., unconscious. Temperature, 109°; pulse, 140; respiration, 28. Treatment: Tub; bled eight ounces; intravenous injection; normal salt solution 600, and hypodermically 400 c.c. In an hour and a half tempera-

ture fell to 96.2° by rectum, but rallied by stimulation to 105°. Eight hours after admission was able to talk rationally, and did well for three days, with normal temperature; pulse good and respiration normal. On the fourth day a diffuse cellulitis of face developed, and he died in twenty-four hours.

Of the cases reported, two appeared to be distinctly benefited by the treatment and became quieter and rational. Both were bled and given salt solution freely, one by the skin and the other intravenously. Both were tubbed immediately. Curiously both developed septic conditions, a phlebitis and a cellulitis, of which one died two days after convalescence from the heatstroke had begun.

Four cases did not rally, and died within twelve hours after admission. Three of these were bled, all received salt solution freely, and were tubbed. The treatment did not appear to have any marked effect except to bring down the temperature.

Oxygen was given continuously in one of the rapidly fatal cases. Its use was suggested by the extreme cyanosis and shallowness of the respirations. It had no apparent effect.

In every case in which phlebotomy was done the blood was dark and thick, and flowed slowly. Nitroglycerin was given hypodermically in two of the rapidly fatal cases, without apparent effect.

We do not feel that any very definite information as to the comparative value of bleeding and the use of salt solution in the treatment of heatstroke can be drawn from the cases here reported. We believe that these measures are theoretically the proper treatment, but it is very difficult to tell whether the improvement observed in Cases I. and III. was due to the reduction of the temperature by tubbing or to the phlebotomy and hypodermoclysis, or to both combined

DR. PACKARD: The employment of saline solution in insolation was tried on pure theoretical grounds, but the opinion of all of us who had to do with these cases last summer was that it was a distinct addition to our other measures of treatment. The determination of the value of any measure in a class of cases so severe as are cases of insolation with very high temperature must always be difficult, and it is impossible by figures, or even by the recital of individual cases, to justly estimate the value of a measure of treatment. In comparing our severe cases last summer with similar series of previous years, it seems undoubtedly the case that the introduction of normal saline solution saved cases that otherwise would have died.

ANEMIA SPLENICA.

[Second Paper.]

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The question of the existence of a separate malady, anemia splenica is still in what may be called the tentative or inquisitive stage. The proposition which I offer for discussion is, that a special malady does exist, of unknown etiology, characterized by a chronic course, enlargement of the spleen, anemia of a secondary type, a marked tendency to hemorrhage from the stomach, and a liability in the late stages to be associated with jaundice, cirrhosis of the liver, and ascites. The conditions described as primitive splenomegaly and Banti's disease are initial and terminal stages, respectively, of this malady. The history of the question I need not discuss, as it is very fully given in the papers of Sippy[1] and of Wentworth.[2] Nor is it necessary to discuss the possible connection of the malady with Hodgkin's disease or pseudoleukemia, with which a majority of observers rightly consider it has nothing whatever to do. In January, 1900, I reported a series of cases.[3] In the present paper I shall give (1) a few additional cases and the subsequent history of several of those previously reported; (2) an analysis of a series of cases of anemia with enlarged spleen, furnished by members of the Association, and (3) a summary of the clinical features of the disease.

I.

The subsequent history of some of the cases in my previous paper may first be given:

[1] American Journal of the Medical Sciences, November, 1899.
[2] Boston Medical and Surgical Journal, 1900.
[3] American Journal of the Medical Sciences, 1900, vol. cxix.

CASE X.—A man, aged thirty-nine years, was first seen June 15, 1898, with moderate enlargement of the spleen, moderate corpuscular anemia, low hemoglobin, and marked pigmentation. He did not know for exactly how long he had had the anemia or the enlarged spleen. I heard from him March 27, 1902. He had been in fairly good health, except that in March, 1901, he had three hemorrhages from the stomach, which, he says, nearly killed him. He was unconscious and in a state of torpor for two weeks. Following this, he had ascites, and had to be tapped. At the date of writing he said he had recovered sufficiently to be able to do his work.

CASE XIV.—A man, aged thirty-five years; a very typical instance, with a greatly enlarged spleen, characteristie blood condition, slight pigmentation of the skin, attacks of hematuria, with slight jaundice. He was last seen on April 16, 1900. The spleen was enlarged; he had been jaundiced for two weeks; edge of liver could be felt 6 cm. from the ensiform cartilage; the right lobe only felt on deep inspiration. He has been under Dr. Thayer's care, who reports this spring that he is still anemic, but able to be at work.

CASE XIII.—Mrs. C. was of exceptional interest, as there was a doubt as to whether the case was not one of pernicious anemia, with greatly enlarged spleen. She did well in the hospital, the spleen reduced in size in a remarkable way. She left the hospital November 20, 1899. She remained well during 1900. The spleen was not below the costal border. She was readmitted in April, 1901, in a condition of the most profound and progressive anemia, in which she died on the 26th. The blood had all the features of a pernicious anemia. The spleen weighed only 400 grams, and the pulp was soft and flabby. There was fatty degeneration of the heart. The liver weighed 1500 grams. The bone-marrow was of a deep gray-red color. The blood condition on her first admission (see first paper), the remarkable improvement with rest and arsenic, the complete disappearance of the symptoms, and the enlargement of the spleen, the relapse, with profound and fatal anemia, leave no doubt, I think, that this belongs to a group of cases of pernicious anemia with enlarged spleen, and does not come in the category of chronic cases here considered.

CASE V.—Male, aged thirty-eight years; seen first November 10, 1898. For nearly twelve years he had had recurring hemorrhages. He returned to the hospital in January, 1900. Dr. Cushing removed the spleen. He did well for ten days, and then had a severe, uncontrollable hemorrhage from the stomach, which proved fatal. On postmortem there were found (1) a practically normal condition of the viscera; (2) moderate cirrhosis of the liver, and (3) esophageal varices, from one of which the last bleeding had occurred. The spleen showed a condition of chronic hyperplasia. In this extraordinary case the enlarged spleen had existed for fourteen years, and he had had throughout the period recurrent hemorrhages.

NEW CASES.

CASE XVI. *Clinical summary: Enlarged spleen and marked pallor for nine years; four severe attacks of hematemesis; removal of spleen; uncontrollable*

hemorrhage; death.[1]—Frederick G., aged thirty years; referred to me by Dr. W. W. Johnston, January 14, 1901. The patient had lived in Washington all his life. When a boy at school he had chills and fever. He has had no attacks within ten years. For years he has been pale. He has, however, been able to attend to his work, and has been active and energetic. He is married. In 1892 it was first noticed that he had an enlargement in the abdomen. This was recognized by Dr. Johnston and others to be the spleen. It had caused him no inconvenience except for an occasional attack of pain in the side. He has had four severe attacks of hemorrhage from the stomach, the first in November, 1896, the second in November, 1897, the third in August, 1900, and the fourth on December 17, 1901, from which he is just recovering. Dark and bloody stools were often noticed after the attacks. They were of great severity. In the one in November, 1897, he had repeated hemorrhages, and very nearly died. He did not recover for nearly five months. Apart from the hemorrhages, his health, on the whole, has been good. The appetite and digestion had been normal and the bowels regular. He has never had a high color, but has had a curious gray pallor, with slight diffuse pigmentation, which has increased of late. His average weight has been 133 pounds. The spleen was enormous, almost filling the left half of the abdomen. The liver was not enlarged.

He was urged by Dr. W. W. Johnston to have the spleen removed, in which opinion I concurred, and he was admitted to the hospital for preparatory treatment. The blood showed red blood corpuscles, 3,300,000; white blood corpuscles, 2400; hemoglobin, 30 per cent.; moderate poikilocytosis; no nucleated reds. Between February 14th and April 14th he gained thirty pounds in weight! The blood improved, rising gradually until on April 5th the red blood corpuscles were 5,200,000 and the hemoglobin 75 per cent. On April 15th Dr. Halsted operated. After ligature of the splenic vessels great difficulty was met with in controlling the hemorrhage from the large veins passing to the stomach—vasa brevia—some of which were as large as the little finger. He lost so much blood that death took place a few hours after the operation. There was no autopsy. The liver, seen at the time of the operation, was smooth, and did not look cirrhotic.

CASE XVII. *Clinical summary: History of malarial fever eighteen years ago; tumor of left side of eleven years' duration; in* 1898 *an attack of severe anemia, with ascites; recovery; in* 1900 *a second attack, with jaundice, anemia, and ascites; gradual recovery; in* 1901 *a third attack, with jaundice, ascites, profound anemia; recovery.*—Minnie W., aged forty years, was first seen in 1898, when she was admitted to Ward O on August 3d (Med. No. 8864), with great swelling of the abdomen and anemia. She had been a healthy woman, married, three children—the youngest eighteen years old. She has always lived in Baltimore. In 1890 she had chills and fever through the summer, and they recurred for several years. She has noticed a hard mass in the left

[1] The surgical and pathological aspects of Cases IV., V., and XVI. will be considered in a separate paper by Drs. Cushing and Macallum.

side of the abdomen since 1890. On the first admission, August 3d, there was no jaundice. She had a greatly distended abdomen, edema of the ankles, and an extreme anemia. The red blood corpuscles were 2,500,000; hemoglobin, 47 per cent.; white blood corpuscles, 1500. There were no malarial parasites; no pigment in the blood. The dropsy subsided rapidly, and it was then found that the spleen reached 18 cm. from the costal margin. A differential count of 525 leukocytes gave small mononuclears 21, large mononuclears 5, polymorphonuclears 67, eosinophiles 2.6, transitionals 1.9. Two nucleated reds were seen. With iron, good food, and open-air treatment (eight to ten hours daily) she improved rapidly, and on September 30th she left the hospital with the condition of the spleen unchanged, but with the red blood corpuscles at 3,500,000; white blood corpuscles, 2400; hemoglobin, 58 per cent. The edge of the liver could be felt 3.5 cm. below the costal border, "soft and slightly tender."

Second admission August 10, 1900, with jaundice, anemia, and ascites. The jaundice had come on about three weeks previously. She has been pretty well for two years, and had been at work. The abdomen measured 92 cm. She was anemic. Red blood corpuscles, 3,800,000; white blood corpuscles, 2000; hemoglobin, 65 per cent. The ascites quickly disappeared and the jaundice lessened. She had two transient attacks of fever. There were no parasites in the blood, and no pigment. She left the hospital November 10, with red blood corpuscles at 4,600,000; white blood corpuscles, 7000; hemoglobin, 70 per cent. The liver reached 3 cm. below the costal margin in the nipple line, and was very tender.

Third admission September 30, 1901, with jaundice, moderate ascites, and anemia. She had kept pretty well since last note. Two weeks before admission she had nausea and vomiting and a chill. With the exception of the deeper jaundice her condition was a good deal better than at the last admission. The abdomen was large and contained a good deal of fluid. The spleen reached 5 cm. below the navel, and the edge was 18 cm. from the costal border. Red blood corpuscles, 3,800,000; white blood corpuscles, 4200; hemoglobin, 58 per cent. As the fluid reduced the liver could be felt just below the costal border in the nipple line, and I noted on October 4th the "edge can be distinctly felt; it is very hard and feels cirrhotic." The jaundice was marked, and there were dilated venules on the face. She again improved, and on October 26th the red blood corpuscles were 4,700,000; white blood corpuscles, 3000; hemoglobin, 62 per cent. The spleen was unchanged. On October 5th a differential count of 500 leukocytes gave, polymorphonuclears 80.6, small mononuclears 9, large mononuclears 5 8, transitionals 3.4, eosinophiles 1.2.

CASE XVIII. *Clinical summary: Enlarged spleen first noticed fifteen years ago; attacks of abdominal pains; marked pigmentation; slight enlargement of the liver; jaundice and secondary anemia; slight fever; marked improvement.*—A. L. W., aged thirty three years; admitted December 27, 1901 (Med. No. 13,848), with jaundice and slight fever. Inflammatory rheumatism fifteen years ago; ulcers on the right leg afterward. Sixteen or seventeen years ago

had chills and fever. He went to Mexico, and while there was jaundiced and sickly for eight or nine months. He returned from Mexico fifteen years ago, and the doctors told him he had an enlarged spleen, which has persisted ever since. He has had gonorrhea, but has not had syphilis. He has been a moderate drinker. He does not think the spleen has increased much in size since it was first noticed. He has been pale for years; he has had occasional attacks of pain, and often a sense of discomfort after eating. For some time he has been losing in weight and feeling badly. His normal weight is 145 pounds; on admission it was 127 pounds. He has lately had cough, with fever and sweats.

On admission Dr. McCrae made the following note:

"His color is striking; he is exceedingly sallow. There are numerous areas of pigmentation over the face and forehead; there is definite jaundice. The patient is sweating profusely; tongue slightly coated; gums and mucous membranes rather pale.

"*Thorax.* Well formed, rather rounded. Expansion good; seems equal. Percussion note clear throughout; everywhere hyperresonant. Breath sounds seem clear throughout.

"*Heart.* There is rather a diffuse impulse. Point of maximum impulse, fifth left interspace, 155 cm. from mid-sternal line. Cardiac dulness begins at third right, opposite fourth interspace; extends 3 cm. to right and 11 cm. to left of mid-sternal line. Impulse well felt; no thrill. At apex the first sound completely replaced by soft murmur, carried to axilla. In fourth interspace there is a suggestion of a sound. On passing upward the systolic bruit increases in intensity, reaching a maximum in aortic and pulmonary areas. It can be heard on both sides out to about the nipple line; is loudly heard over the vessels of the neck. In the third left interspace close to the sternum the systolic murmur has a very rough quality. The second sound everywhere is soft. No definite diastolic murmur is made out. In aortic area has a murmurish quality. Pulse 24 to quarter, of fair tension, regular, of suggestive collapsing quality; there is a quick rise. Pulse is not that of aortic stenosis.

"*Abdomen.* Slightly full; no special visible prominence; no rose spots; walls fairly soft. Spleen very readily palpable; extends 12 cm. from the left costal margin, and comes to within 4 cm. of the navel and 5 cm. of the left anterior superior spine. It is hard, slightly tender, and slightly movable. Liver apparently also enlarged; in median line the edge being 5 cm. above the navel, and in the right nipple line 4 cm. below the costal margin. In the right nipple line dulness begins at the fifth right and extends 12 cm.; in the mid-axillary line dulness begins at the fifth interspace. The patient's body not specially pigmented, though dark; no special pigmentation about the nipples.

"Hemoglobin, 53 per cent.; red blood corpuscles, 3,026,000; white blood corpuscles, 6875. Differential count; Jenner stain. Red cells show marked poverty in hemoglobin, marked variation in size, there being many microcytes, no macrocytes, some poikilocytosis. In counting 536 cells no nucle-

ated reds seen. Count in general shows relative increase in mononuclear elements; polymorphonuclears, 55.96; large mononuclears, 29.85; small mononuclears, 11.19; transitionals, 2.23; eosinophiles, 0.37; mastzellen, 0.37."

For five days his temperature ranged between 100° and 101°, and he had a soft friction murmur in the left axilla. He had a small quantity of sputum, which was repeatedly examined for tubercle bacilli, with negative results. He gradually improved, the jaundice lessened, but there seemed to be an increase in the general pigmentation of the skin. By February 1st the patient was very much better. On the 2d, red blood corpuscles, 3,600,000; hemoglobin, 65 per cent.

He was discharged February 7th, still looking rather pigmented, but free from fever, and having gained six pounds in weight. The urine contained bile at first, but was otherwise normal. The spleen was unchanged.

II. Incidence of Enlarged Spleen with Anemia.

While the combination seems to be not infrequent, yet cases reported in the literature as splenic anemia are rare. Rolleston, in his recent paper,[1] states that he has been able to collect only thirty-seven cases. In February last I sent a circular letter to members of the Association asking for information on the subject, and for notes of unpublished cases. I am indebted to twenty-four physicians for notes of forty-five cases, which I have grouped as best I could. It was not always possible to classify the cases properly, as in some no information was given as to the duration of the disease.

1. *Acute Anemia, under One Year's Duration, with Enlarged Spleen*, 12 cases.[2]

In none of the cases was there a history of malaria, the duration of the illness ranged from eleven weeks to twelve months. The size of the spleen was not always stated. In the cases of A. O. J. Kelly and J. C. Wilson it was only two fingers' breadth below the costal border; but in the cases of Cary, Edwards, Blackader, and Rotch the organ was greatly enlarged. In eight of the cases the red blood corpuscles were below 2½ millions per cubic millimeter. In the cases of Musser and Blackader the count sank below one million per cubic millimeter. The hemoglobin was relatively low in six cases, of normal proportion in two, plus in two, and not given in two cases.

The leucocytes were under 6000 per centimeters in eight cases; in three of these, below 2500. In two they were about normal, and in

[1] Clinical Journal, 1902.

[2] Abstracts will be found in the appendix.

only two above normal, in one 7000 per cubic millimeter, and in one 20,000 per cubic millimeter.

In some of these cases the history, course, and blood condition suggest progressive pernicious anemia. Case XIII., reported in my first paper, had, as I then remarked, many of the features of this disease. She returned (as noted in the early part of this article), and died with all the features of a pernicious anemia, plus great enlargement of the spleen. This group is of unusual interest, and brings up the question of the frequency of enlarged spleen in pernicious anemia. Hunter[1] says "in a certain number of instances the spleen has been found enlarged, this condition being even recognizable during life." He mentions a number of cases reported by different observers; the largest mentioned "was in a case reported by Wilks (500 grams). In four cases of his own, the spleen weights were 19 ounces, 11 ounces, 10 ounces, and 13 ounces." In a great majority of the cases the spleen is either described as normal or no mention is made of the condition at all. Cabot[2] notes enlargement in 13 of 110 cases; Billings[3] in 5 of 20 cases. Among 40 cases from my wards, reported by McCrae[4] "the spleen was felt in only 6 cases, and in none of them was the enlargement at all marked, it being noted that 'the spleen was just felt.'"

2. *Chronic Anemia, with Enlarged Spleen*, 26 cases.

Eighteen of these were in males. The duration of the disease is most interesting; eleven years, 1 case; nine, 1; eight, 1; seven, 3; six, 2; five, 1; three, 2; four, 1; two, 3; between one and two years, 3; in 1 doubtful, "many years." In 9 of the cases the disease had lasted for more than five years; in 7 the duration was unknown. Hematemesis occurred in 9 cases, jaundice in 4 cases, ascites in 5, and in 7 cases the liver was enlarged. Several of the cases had been regarded as Banti's disease, or the terminal stage of anemia splenica.

In only 7 of the cases were the red blood corpuscles below 2,500,000 per cubic millimeter. In 22 cases the hemoglobin percentage was relatively low, in 3 it was normal, and in 1 it was not given. In 13 cases the leukocytes were below 5000 per cubic millimeter. In a

[1] Pernicious Anemia (monograph), 1901.
[2] American Journal of the Medical Sciences, 1900, p. 1.
[3] Ibid.
[4] Journal of the American Medical Association, 1902, i.

case of Vickery's they were only 650 to 700 per cubic millimeter, and in Peabody's case they were only 800 per cubic millimeter, and the highest of several counts in this case was 1400. In 3 cases they were above 7000 per cubic millimeter, and in 9 cases they ranged from 5000 to 7000 per cubic millimeter.

3. *Simple Splenomegaly*, 2 cases.

Two cases were returned as simple or primitive splenomegaly. In Dr. Herrick's case the normal red count and the relatively low hemoglobin, with a history of ill-defined symptoms for five years, suggest the early period of splenic anemia. In Drs. Blackader and Martin's case the enlarged spleen was found after an accident in which the man was knocked breathless. He vomited dark material. The spleen has gradually increased in size. There is practically no anemia.

There were three cases difficult to classify, and in two cases other diseases were presented—cirrhosis of the liver and sarcoma of the spleen. (See Appendix.)

III. Anemia Splenica Chronica.

Definition. *A chronic affection, probably an intoxication of unknown origin, characterized by a progressive enlargement of the spleen which cannot be correlated with any known cause, as malaria, leukemia, syphilis, cirrhosis of the liver, etc. (primary splenomegaly); anemia of a secondary or chlorotic type (leukopenia), a marked tendency to hemorrhage, particularly from the stomach; and in many cases a terminal stage, with cirrhosis of the liver, jaundice, and ascites (Banti's disease).* It seems probable that the conditions separately described in the literature as primitive splenomegaly, splenic anemia, splenomegalic cirrhosis of the liver, or Banti's disease are stages of one and the same malady. Let me first give a brief analysis of the cases which have been under my care which conform to the above definition. I have cut out Cases I. and II. of my first series, as they were seen long ago (1879), though both patients had enlarged spleen and hematemesis; but I am uncertain about the duration and etiology. Case XIII. I have also discarded as probably progressive pernicious anemia with greatly enlarged spleen. This leaves a group of fifteen cases, seen within the past ten years; all have been carefully studied, and the full report of the blood condition will be found

in the *Edinburgh Medical Journal*, May, 1899, and in the *American Journal of the Medical Sciences*, January, 1900, and in the present paper.

ABSTRACT OF FIFTEEN CASES.

CASE III.—Male, aged thirty-five years; duration twelve years. Enormous spleen; recurring attacks of hematemesis and melena; pigmentation of the skin; death after an attack; no cirrhosis of the liver. Blood count lost.

CASE IV.—Male, aged thirty-three years; duration ten years. Recurring attacks of hematemesis and melena; enormous spleen; pigmentation of the skin; removal of the spleen; liver not cirrhotic; recovery. Red blood corpuscles, 3,000,000; hemoglobin, 25 per cent.; leukocytes, 2800.

CASE V.—Male, aged forty years; duration thirteen years. Recurring attacks of hematemesis; occasional melena; enormous spleen; grayish-brown pigmentation of the skin; slight ascites; removal of the spleen; liver moderately cirrhotic; death from rupture of esophageal varix. Red blood corpuscles, 4,000,000; hemoglobin, 30 per cent.; leukocytes, 6500.

CASE VI.—Male, aged twenty years; duration eleven years. Onset with hematemesis; pigmentation of the skin; spleen very large. Red blood corpuscles, 2,187,000; leukocytes, 12,497.

CASE VII.—Male, aged forty years; duration two years. Enormous spleen; recurring cutaneous hemorrhages; remarkable pigmentation of the skin. Red blood corpuscles, 4,816,000; hemoglobin, 55 per cent.; leukocytes, 5000.

CASE VIII.—Female, aged fifty-six years; duration three years. Spleen very large; no hemorrhages; no pigmentation. Red blood corpuscles, 3,600,000; hemoglobin, 60 per cent.; leukocytes, 3000.

CASE IX.—Male, aged fifty-eight years; duration six years. Spleen very large; recurring ascites; no hemorrhage; no pigmentation; enormous ascites; no cirrhosis of liver; death. Red blood corpuscles, 4,788,000; hemoglobin, 60 per cent.; leukocytes, 5200.

CASE X.—Male, aged thirty-nine years; duration doubtful—more than three years; hematemesis, melanoderma, and leukoderma; spleen greatly enlarged. Red blood corpuscles, 4,128,000; hemoglobin, 45 per cent.; leukocytes, 2800.

CASE XI.—Male, aged fifty-seven years; duration two years. Spleen greatly enlarged; no hemorrhages. Red blood corpuscles, 2,500,000; hemoglobin, 37 per cent.; leukocytes, 3000.

CASE XII.—Male, aged forty years; duration (now) four years. Greatly enlarged spleen; recurring hematemesis; ascites; recovery. Red blood corpuscles, 4,208,000; hemoglobin, 45 per cent.; leukocytes, 4000.

CASE XIV.—Male, aged thirty-five years; duration (now) four years. Hemorrhage from kidneys; no malaria; greatly enlarged spleen; marked pigmentation of the skin. Red blood corpuscles, 3,856,000; hemoglobin, 55 per cent.; leukocytes, 4500.

CASE XV.—Male, aged forty-three years; duration eight years. Very large spleen; recurring hematemesis. Red blood corpuscles, 4,270,000; hemoglobin, 45 per cent.; leukocytes, 2500.

CASE XVI.—Male, aged thirty years; duration ten years. Recurring hematemesis; grayish-brown pigmentation of the skin; removal of spleen; no cirrhosis of liver; death. Red blood corpuscles, 3,300,000; hemoglobin, 30 per cent.; leukocytes, 2400.

CASE XVII.—Female, aged forty years; duration ten years. Recurring attacks of acute anemia, with jaundice and ascites; enormous spleen; no hemorrhages. Red blood corpuscles, 3,500,000; hemoglobin, 53 per cent.; leukocytes, 2400.

CASE XVIII.—Male, aged thirty-three years. Duration of enlarged spleen fifteen years; organ greatly enlarged and liver enlarged; slight jaundice; marked pigmentation of the skin; no hemorrhages. Red blood corpuscles, 3,326,000; hemoglobin, 53 per cent.; leukocytes, 6875.

As in the cases collected by Rolleston, the *sex* in my series shows a great prevalence among males—thirteen to two. All of the cases were in adults, chiefly in young adults; in one only (Case VI.) had the disease begun in childhood.

There is nothing in the *etiology* of the cases to throw any light on the causation. The question of *malaria* naturally arises, considering the locality in which I practise. There was a history of malaria in five cases. In three of these (aged 40, 56, and 30 years) the infection was in childhood. In only two (Cases XVII. and XVIII.) had the infection occurred in adult life—one twelve years before onset of illness, the other eighteen years before. The locality has nothing to do with the number of cases observed; only five cases came from Maryland, four of which were from the city of Baltimore. The others came from New York, Pennsylvania, Illinois, Massachusetts, West Virginia, Virginia, North Carolina, South Carolina, Canada, and Jamaica.

Heredity has played no part in my cases, but Brill[1] has reported three cases in one family. One girl died, aged nine years, with enlargement of the spleen. The description of the other two cases leaves no doubt, I think, that they belong to the disease under discussion. Case III., with the peculiar pigmentation, the tendency to hemorrhages, and the type of anemia present, corresponds exactly with chronic splenic anemia. Bovaird[2] has described a similar condition in

[1] American Journal of the Medical Sciences, April, 1901.
[2] Ibid., October, 1900.

two sist ers; a sister of Collier's[1] patient died with enlarged spleen, while C. Wilson[2] has reported a family in which in three generations six members had enlarged spleen. It is quite possible that all of these cases belong in the category of chronic splenic anemia.

SYMPTOMATOLOGY. 1. *The Remarkable Duration of the Disease.* Among disorders of the blood or blood-making organs anemia splenica is characterized by an extraordinary chronicity. In some of the cases in my series the disease had lasted more than twelve years. Rolleston reports a case of twelve years' duration, beginning in the eleventh year, the condition remaining throughout very much the same, except that during the last three years of life there was recurring hematemesis. Senator[3] and others have noted this peculiarity. An extraordinary illustration I saw last winter in New York with Dr. Walter James, who will report the case in full. The patient had had an enlarged spleen, with anemia of varying intensity, for at least twenty-five years. He died at last in a profound anemia, with ascites. Gaucher's case of splenic enlargement existed for twenty-five years. In my series of fifteen cases, in seven the duration of the disease was more than ten years, and in eleven, more than four years.

In ten of the twenty-six cases of chronic splenic enlargement, with anemia, under the care of my colleagues in the Association, the disease had lasted more than five years. It is strange how slight may be the inconvenience, even with a spleen extending below the navel. A majority of my patients were active business men, and, as in Cases III. and XVI., the chief trouble was the recurring hematemesis and the protracted up-hill convalescence after the attacks.

2. *The Splenomegaly.* There are many conditions in which the spleen may be enlarged for months or years, sometimes without any apparent injury to health. I have had a group of cases of moderate enlargement of the spleen in women, without obvious cause and without marked anemia, in which the discomfort of the movable organ was the chief complaint. Two of these cases have remained well for years, having had the organ "packed" into position. Among the dark-skinned emigrants from southern and eastern Europe and from Armenia moderate enlargement of the spleen is not uncommon

[1] Pathological Society Transactions, vol. xlvi.
[2] Clinical Society Transactions, vol. xxiii.
[3] Deutsches Archiv f. klin. Med., 1901.

—a point noted by Cabot in the discussion of this paper. It may be a manifestation of latent paludism.

In the very large group of cases of splenomegaly, with secondary anemia:

(*a*) The cause is usually apparent—malaria, tuberculosis, rickets, or syphilis—particularly in children, in whom any state of malnutrition, if protracted, may be associated with enlargement of the spleen.

(*b*) The anemia and splenomegaly usually yield to appropriate treatment; at all events there is not the remarkable chronicity.

(*c*) The spleen in this group rarely reaches the colossal size seen in chronic splenic anemia.

(*d*) The sequences so characteristic of splenic anemia are not seen.

(*e*) While the blood shows the features of a secondary anemia, there is rarely the exaggerated chlorotic type, and leukocytosis is more common than leukopenia.

There are many gaps in our knowledge, and it is difficult to assign to individual cases their proper places. It may not always be possible to speak definitely. For example, in the case of James P., aged four years, sent by Dr. Rotch (No. 12, acute cases), with a large spleen and a marked anemia, with leukopenia of two months' duration, where shall we classify it? or a case, sent by Cabot, of a child aged seven months, duration of illness not stated, with red blood corpuscles, 3,200,000; hemoglobin, 25 per cent.; leukocytes, 36,800, and nucleated red blood corpuscles 6190 per cubic millimeter. The anemia is more or less acute, the splenomegaly moderate, and the blood condition may be very variable. On the other hand, many of the cases in children conform to the definition above given of chronic splenic anemia. Another case of Rotch's (No. 18 in chronic series): at the age of three years the spleen and liver were large, the anemia was marked; nine years later the spleen was enormous, the liver still enlarged, the anemia pronounced, and the skin was pigmented.

The special feature of the enlarged spleen in chronic splenic anemia is the size, which is unequalled in any other disease except, perhaps, leukemia. The abdomen may be enormously distended, and the organ may not only occupy the left side, but may curve upon itself and pass across to the right iliac fossa and the right flank. The notches may be directed upward, as in one of Collier's cases which I saw with him at the Radcliffe Infirmary, Oxford, in which the

border of the spleen and the notches were between the navel and the ensiform cartilage. The average weight in twelve cases collected by Rolleston was sixty-one ounces. In Bovaird's case the organ weighed twelve and one-half pounds. The mechanical discomfort may be considerable, though as a rule there is very little pain unless perisplenitis be present, in which case a friction may be felt or heard. In Rolleston's case a *bruit de diable* was heard over the organ.

Many of the cases reported in the literature as primary or primitive splenomegaly come under the definition of the disease as given above. In the chronicity (eleven and fifteen years and thirteen years) and in the general features the cases of Brill and of Bovaird conform to chronic splenic anemia.

3. *Hematemesis* is a remarkable feature of the disease. Eight of my patients had attacks of vomiting of blood. In Cases I. and II. (which I have discarded from my series as seen in 1879 and deficient in certain details) the hemorrhages were most profuse. I have never seen such enormous losses of blood as in Case II. In the nineteen cases communicated by members of the Association, hematemesis occurred in seven. In a large proportion of the cases the hemorrhage is due to conditions associated with the enlarged spleen, not to accompanying cirrhosis of the liver. In Cases IV. and XVI. of my series the spleen was removed, and at the operation the liver was seen to be normal. In Case III. it was not cirrhotic postmortem. It is easy to understand this splenic origin, as 40 per cent. of the blood from the stomach passes by the vasa brevia to the splenic veins. (Mall and Krauss.) Watson gave a mechanical explanation (which I have quoted in my first paper) of the bleeding. The source of the blood may be (*a*) a general diapedesis from the gastric mucosa. This is doubted by some writers, but on several occasions I have not been able to find, after a most careful search, either minute erosions of the mucosa or ruptured veins in the esophagus, and there seems to be no other explanation; (*b*) small erosions of the gastric mucosa; (*c*) rupture of a varicose vein of the esophageal plexus, which was the cause of death in Case V. after removal of the spleen. The recurring profuse bleedings may very often be from this source, considering the intimate relation between the veins of the fundus of the stomach supplying the vasa brevia and those of the cardiac orifice and the esophagus; (*d*) Rolleston suggests that the large wandering spleen

may pull on the gastrosplenic omentum and give rise to torsion of the veins, or cause a kink in the splenic vein, and so induce intense venous engorgement of the stomach.

With the exception of the chronic hemorrhagic form of the peptic ulcer there is no known condition in which hematemesis may occur for so many years. In Preble's[1] study of gastrointestinal hemorrhages in cirrhosis of the liver, in five of the thirty-five cases in which esophageal varices were found the hemorrhages had occurred at intervals varying from a few months to five years.

Hemorrhage from other sources is less frequent. Epistaxis may recur at intervals; retinal hemorrhages, bleeding gums, menorrhagia, and hematuria have been recorded. Purpuric attacks, as in Case VII. of my series, may occur.

4. *Anemia.* Even in well-defined cases the anemia may be slight. As in locomotor ataxia there may be no ataxia, so in anemia splenica there may be no corpuscular anemia—a point which may be urged against the use of these names. Take, for example, Case XVI., here reported. Prior to the operation there was no anemia of corpuscles, which were 5,200,000 per cubic millimeter, but he was still pallid and had only 75 per cent. of hemoglobin, and there was not the slightest change in the spleen; yet he presented a most typical picture, and anyone who had seen Cases III., IV., and V. could have recognized at a glance that the case belonged, with them, to a separate clinical group, quite as definite as leukemia or Addison's disease. Very few of the patients will be found to have a normal amount of hemoglobin; they are constantly "off color."

There is nothing peculiar or distinctive in the anemia, which is of the secondary or chlorotic type.

(*a*) *The corpuscular anemia* is of a moderate grade. Of the fifteen cases of my series the average was 3,425,000 per cubic millimeter. The lowest blood count was 2,187,000; the highest count was 5,200,000, in the patient just referred to.

(*b*) *The low hemoglobin* is an interesting feature and rather more striking than in other secondary anemias. It is certainly rare, except in chlorosis, to find a patient with obvious anemia and a blood count (corpuscles) normal or even, as in Case XVI., above normal. The average of thirteen hemoglobin counts was 47 per cent.

[1] American Journal of the Medical Sciences, January, 1901.

(*c*) *Leukocytes.* Immediately after a profuse hemorrhage, or in a terminal affair, there may be a leukocytosis, but, as a rule, there is a leukopenia. Of 14 cases the average leukocyte count was 4520 per cubic millimeter. If we leave out Case VI., admitted shortly after a severe bleeding, with a leukocytosis of 12,500, the average of 13 cases —in one of the series (III.) the blood count was mislaid—was 3850 per cubic millimeter.

In the extreme anemia which may come on at the close there may be marked poikilocytosis, with nucleated red corpuscles, etc. There has been nothing characteristic in the differential count of the leukocytes.

5. *Pigmentation of the skin* is a common event in the very chronic forms, having been present in eight of my cases. A majority of these presented the usual bronzing of the skin, diffuse in character, and resembling that seen in Addison's disease, though rarely so intense. In some it was a curious steel-gray staining of the skin, of a very peculiar character, suggesting rather argyria than the usual form of melanoderma. In some cases it was patchy and associated with areas of leukoderma.

Pigmentation of the skin seems to be a common feature in the long-standing cases, and has been commented upon by Brill, Bovaird, Frederick Taylor, and others. It is of special interest in connection with the melanoderma of hemochromatosis (bronzed diabetes) and of Hanot's cirrhosis. In Case XIV. of the series a portion of the skin did not show the ochre-brown pigment such as is present in hemochromatosis. It is to be borne in mind that arsenic is used largely in these cases, and it is quite possible that to it in part may have been due the dark color of the skin. In no case were there keratoses.

6. *Hepatic Features.* The mutual relations of diseases of the spleen and liver are well illustrated in splenic anemia. While a majority of the cases present no symptoms of disturbed action of the liver, and in a few the occurrence of ascites, even when the liver is normal, suggests cirrhosis, there is a third group in which the hepatic features so predominate that cirrhosis of the liver is at once suspected. Hematemesis is a splenic, not an hepatic, feature of the disease. Cases IV. and XVI., in which the hemorrhages had occurred for many years, presented at the time of operation a normal liver. Case IV. was alive and well (having had no recurrence of the hemorrhage) nearly three years subsequently. While hemorrhage from the stomach may be a

very early, indeed the very first, symptom of cirrhosis of the liver, it is most unusual to have recurrences over long periods, as in the cases recorded in this series. Even in the more chronic type of cirrhosis—Hanot's variety—hematemesis is not so special a feature as in splenic anemia. In the later stages of the disease the cirrhosis of the liver, if present, as in Case V., may aggravate the conditions favoring hemorrhage. In my series hepatic features have not been very marked.

Ascites occurred in four cases. In Case V. it was slight and associated with edema of the ankles. The patient had had shortly before readmission a series of bleedings. At the operation, and ten days subsequently at autopsy, slight cirrhosis of the liver was found. In Case XVII. ascites was present at the time of the admissions, August 3, 1898, August 10, 1900, and September, 1901. In each instance it disappeared with the general improvement. In the second and third admissions there was jaundice. The liver was slightly enlarged and felt cirrhotic. In Case XII. there was no dropsy when I saw him, but six weeks before six quarts were drawn off. Dr. Vickery writes that he had been tapped again. The liver was not enlarged. In Case IX. there was ascites in 1895, again in 1897, and a third time in his final illness, in the spring of 1898. The liver could be felt a little below the costal border, but at the postmortem there was no cirrhosis.

In the series of cases of anemia, with enlargement of the spleen, sent by my colleagues, ascites was present in the cases of McPhedran, Edes, Atkinson, Sears, and Cabot; in two of the cases in association with jaundice.

Jaundice was present in only two cases in my series and in four in the association series.

State of the Liver. In eight cases the liver was of normal size. In Cases IV. and XVI. the organ was seen to be smooth and natural looking at the time of operation. In Cases III. and IX. it was normal postmortem. In six cases it was slightly enlarged; in no case was the organ large and hard, as in forms of hypertrophic cirrhosis. In one case it was reduced in size; in only one (Case V.) was cirrhosis of moderate grade found postmortem. In seven of the cases in the association series the liver was enlarged.

Relation of the Cirrhosis of the Liver to the Enlarged Spleen. Splenomegaly and cirrhosis of the liver are associated in the following conditions:

1. *Atrophic Cirrhosis of the Liver.* So constant is moderate enlargement of the spleen that in doubtful cases it is an important help in diagnosis. The organ is not often very large, rarely reaching to the navel. That it is due to the chronic passive congestion is shown by the remarkable reduction in size which may follow an attack of hematemesis. There is a moderate hyperplasia and often a perisplenitis. Parkes Weber suggests that the enlarged spleen may be due in part to a toxemia.

2. *Syphilis of the Liver.* Both liver and spleen may be involved in amyloid degeneration, but the cases in question are gummata of the liver with consecutive contraction. The spleen may reach a very large size. A remarkable congenital case, in a girl twenty-one years of age, occurred some years ago in my wards,[1] in which, in addition to the big spleen and syphilitic liver, there was a high degree of leukocytosis. In my previous paper on splenic anemia I have reported two other cases, and have called attention to the liability of error. In one of the histories sent by Dr. Musser the patient, aged forty-five years, had had syphilis of the brain. In 1898 and 1899 he had jaundice, with great enlargement of the spleen and liver, hemorrhages from the stomach and bowels, and moderate anemia. In Coupland's case[2] an enlarged spleen was removed, and two years later the patient died with hematemesis and ascites; the liver was found to be syphilitic. When we recognize more fully the great frequency of syphilis of the liver[3] and learn the extraordinary diversity of its clinical features we shall find, I think, a very interesting group of cases characterized by irregularly contracted liver, big spleen, and anemia.

In both the alcoholic and syphilitic cirrhosis the liver, as a rule, is small, and *the splenomegaly follows and depends, in great part at least, on the condition of the liver.*

3. *Hemochromatosis.* This remarkable and most obscure affection is characterized by a chronic course, a gradual deposition of an iron-containing pigment in the organs and in the skin (leading to pigmentation), a progressive enlargement of the spleen, hypertrophic cirrhosis of the liver, sclerosis of the pancreas, and, finally, diabetes—the

[1] Johns Hopkins Hospital Bulletin, vol. ii.

[2] British Medical Journal, 1896, vol. i.

[3] See recent papers by Einhorn, Medical Record, 1901, and Stockton, Journal of the American Medical Association, 1902, vol. ii.

bronzed diabetes of the French. Anschutz[1] and Opie[2] regard the affection as a chronic toxemia leading to hemolysis, with gradual deposition of blood pigment in the organs (leading to sclerosis) and in the skin. There may be a marked tendency to hemorrhage (purpura). In the cases I have seen the spleen has not been enormously large,[3] and the condition is one in which *the splenomegaly and the cirrhosis of the liver go hand-in-hand*, both apparently due to the same cause.

Anemia, so far as I can learn, has not been a special feature of the cases. It is of interest to note that in the case which was reported by H. A. Hare as Banti's disease, and which had been under the care of Musser and J. C. Wilson (Case I., *Chronic Cases*, in Appendix) the patient, who had been ill for seven years, had a very large spleen, moderately enlarged liver, anemia, and diabetes. No mention is made of pigmentation of the skin.

4. *Other Forms of Cirrhosis.* Apart from the alcoholic and syphilitic varieties, there is a large group of cases in which the disease occurs chiefly in the young, usually the hypertrophic form, and in association with great enlargement of the spleen.

(*a*) *Hanot's cirrhosis*, the best known of these varieties, is a very chronic enlargement of the liver occurring in young persons, sometimes as a family form, not associated with the abuse of alcohol or with malarial or syphilitic infection. The spleen is enlarged, but not of very great size in proportion to the liver. There is a chronic jaundice of varying intensity, a marked tendency to hemorrhage, but not specially to hematemesis, and very often a terminal *icterus gravis*. Rarer features are bronzing of the skin, a marked leucocytosis, and fever. Ascites does not occur (?). The relation in time of the hepatic enlargement, and the predominance of the biliary symptoms from the outset are characteristic features. The lesions are those of a biliary cirrhosis.

(*b*) There is a *simple cirrhosis* of the liver in children, without great enlargement of the liver, moderate splenomegaly, and a clinical picture almost identical with that of the disease in adults. Ascites is a prominent feature. Some of the cases have been of alcoholic origin, but in a majority I think the starting point has been in the changes which have followed one of the fevers of childhood. The

[1] Deutsches Archiv für klin. Med., 1899, Band lxii.
[2] Opie, Journal of Experimental Medicine, vol. v.
[3] British Medical Journal, 1899, vol. ii.

condition is certainly very different from Hanot's cirrhosis, and very different, too, from the third type, (*c*) *splenomegalic cirrhosis*, the form which specially concerns us here on account of its relations with splenic anemia, and which must be discussed as a separate section.

5. *Splenomegalic Cirrhosis of the Liver.* After lasting for some time, splenic anemia may be followed by cirrhosis of the liver. It was the merit of Banti to call attention to this sequence. The splenomegaly may exist for a long period of years without leading to cirrhosis of the liver, as illustrated in Cases III. and IV. of my series. In Case V., after a period of between thirteen and fourteen years, the organ was only moderately cirrhotic. The enlargement, in adults at least, is not very great, and the splenic features dominate the case throughout, and the ascites and hematemesis, as I have insisted, do not necessarily indicate that the liver is involved.

Can we bring into this category the remarkable group of cases in children, particularly the family form of splenomegaly, which corresponds in so many features with chronic splenic anemia? Take, for example, the case reported by Frederick Taylor.[1] The lad, aged thirteen years, had had for six years an enlarged spleen, with jaundice and enlarged liver. There were anemia, melanoderma, hemorrhages, and clubbed fingers. Postmortem the spleen weighed eighty-seven and a half ounces, and the liver, only forty ounces in weight, was rough and nodular. The case is reported as one of splenomegalic cirrhosis. Bovaird's case, already referred to, was one of two sisters affected. At the age of sixteen years, thirteen years after the onset, there was marked anemia, no jaundice, enormous spleen, moderate enlargement of the liver, and melanodermia. The spleen weighed twelve and a half pounds; the liver, sixty-eight ounces, was cirrhotic. In Rotch's case (No. 18 in Appendix) the lad, aged twelve years, had had a big spleen for nine years. When three years old the spleen and liver were enlarged, and there was anemia. Nine years later the spleen was enormous, reaching to the pelvis; there was pigmentation of the skin and extreme anemia, without leukocytosis. In the cases of Edes (No. 8) and Vickery (No. 12), also of long duration in children with enormous spleens—ascites in the one case and hematemesis in the other—the liver was not enlarged.

Some of these are undoubtedly cases of splenic anemia in child-

[1] Guy's Hospital Reports, vol. liv.

hood. The truth is, we need a very careful study of this group of cases before we can speak of them with any certainty. The cases are singularly chronic, and pass from one physician to another. The relation in time of the hepatic and splenic lesions, the forms of hypertrophic cirrhosis of the liver in children, the relation of the family variety to the others, the state of the liver in the cases of primary splenomegaly, the condition of the blood, the relation of the cases to hemochromatosis and to Hanot's cirrhosis—these are some of the questions awaiting solution. I have purposely refrained from using the terms introduced of late years by our French colleagues, whose studies in cirrhosis of the liver have been so important. The long-sounding names simply express the plain fact that the cirrhosis of the liver may precede (as in portal cirrhosis), accompany (as in hemochromatosis), or follow (as in splenic anemia) the splenomegaly. For the last group the term splenomegalic cirrhosis is allowable; but, as Dr. Frederick Taylor says, it is devoutly to be hoped that "we may be delivered from the cumbrous and unwieldy nomenclature which has been suggested for temporary use by our foreign *confrères*."

PATHOLOGY. The morbid anatomy throws very little light on the origin of this remarkable disease. Two conditions have been described in the spleen: 1. A fibrosis and hyperplasia, with atrophy of the pulp and a hyaline degeneration of the Malpighian bodies;[1] and with this description Dr. W. G. McCallum tells me our cases (IV., V., and XVI.) correspond, with certain minor differences. 2. On the other hand, a very remarkable change has been found in certain cases of splenomegaly; cases which, as I have said, agree in every clinical particular with the definition of the disease above given. The normal texture is largely replaced by fibrous tissue and large endothelial cells with clear protoplasm containing two or more nuclei, and among them giant cells. The condition is beautifully shown in the illustration in Bovaird's article. No wonder that Gaucher described it as primary endothelioma, although the spleen had been enlarged twenty-five years. The same structure has been described by Picou and Ramond, Collier, Harris and Herzog, and Rolleston. "It has been suggested by Bovaird that the proliferated endothelial cells eventually form fibrous tissue, and, though Harris and Herzog do not support this, the microscopic appearances certainly are compat-

[1] Banti, Ziegler's Beiträge, Band xxiv.

ible with this view. It is perhaps more probable that the fibrous hyperplasia goes on at the same time as the endothelial proliferation, and is due to the same cause, viz.: a chronic intoxication. The fibrous tissue of the organ contains pigment granules of hemosiderin and hematoidin. . . . In some recorded cases fibrosis and atrophy of the pulp and Malpighian bodies have been the only changes described. It is perhaps possible that in such cases the change has progressed, as it may do, in lymphadenoma to fibrosis and disappearance of the endothelial proliferation" (Rolleston). A point to be emphasized in favor of the view that these two changes of endothelial proliferation and fibrous hyperplasia are part of the same process is the identity of the clinical course in cases in which one or other of the changes has predominated. In Bovaird's patient the splenomegaly had lasted thirteen years; there was marked pigmentation, a secondary anemia, and moderate sclerosis of the liver. In Rolleston's case the enlarged spleen had existed twelve years, and, as already stated, in Gaucher's patient twenty-five years.

The true nature of the disease is unknown. It is probably a chronic toxic rather than an infective process, but of the character and the source of the poison we are ignorant. Naturally, with the prevalence of theories of autointoxication, the origin has been sought in the intestinal tract—among the *fermenta imaginaria*, of which Glisson speaks in the section *de Flatu* of his celebrated *Tractatus de Ventriculo et Intestinis*. Harris and Herzog suggest that a chronic hemolysis is caused by an enzyme manufactured by the endothelial cells of the spleen, but this does not explain the cause of the splenic changes. That the spleen is a most important factor in the disease is shown by the cure which has followed its removal, as though the organ were the seat of the manufacture of some poison; but all this is theory.

NOMENCLATURE. "What's in a name?" may well be asked of the disorder under discussion, to which an unusual number of labels have been attached. The all-important matter is to define as accurately as possible the condition named, according to the good rule laid down by Socrates: "Now, I have no objection to your giving names any significance you please if you will only tell me what you mean by them."[1] If our knowledge does not permit to give a name

[1] Plato's Charmides (Jowett's Plato, vol. i. p. 21).

according with the etiology of the disease, the rule should be to pick the one which seems least objectionable, taking priority and usage into account. To me splenic anemia seems a less objectionable term than *splenic pseudoleukemia*, *splenic lymphadenoma*, *splenic cachexia*, *primitive splenomegaly*, or *Banti's disease*. So far as we know, the primary involvement is of the spleen, though the anemia and the enlargement of the organ may both depend on a common, unknown factor. The name certainly expresses the two most constant features of the affection, though the anemia is not necessarily present throughout. A serious objection is that the term has been used in a generic sense, as under anemia splenica several diseases have doubtless been described; but the condition here described has features so remarkable and definite that to restrict the term to it seems advisable, with the qualifying addition of the word *chronic*. The protracted course of the disease is one of its most extraordinary peculiarities, and serves to separate this group from the acute anemias with enlargement of the spleen. Usage, too, should count, and it is something that the name should have been introduced by a great clinical physician, Griesinger, and has been adopted by such men as Strümpell, Senator, Coupland, Rolleston and others.

The name *primary* or *primitive splenomegaly* has the advantage of neutrality or indifference in not suggesting any theory of origin, and there is no objection to its use in designating cases—such as those reported by Herrick, Martin, and others—in which the enlarged spleen constitutes the only manifestation. *Banti's disease* is simply chronic splenic anemia plus features of cirrhosis of the liver, which represent a terminal stage in the disease. Banti's merit consists in calling attention to this important aspect; but, after all, these secondary changes in the liver are somewhat rare, and, as my records show, the hemorrhages, ascites, and even the jaundice may be present without existing cirrhosis.

TREATMENT. Since my first paper there has been a notable contribution made to the treatment of splenic anemia in the study, by Harris and Herzog,[1] of the results of splenectomy. Of nineteen cases, in fourteen recovery followed; in one the result was not given. In three of my patients, as already stated, the spleen was removed. In Case IV. (operated on by Dr. Cushing) the man, when heard from

[1] Annals of Surgery, July, 1901.

last, three years after the operation, remained well. This man had had at intervals of a year, for ten years, attacks of hematemesis. In Case V. (operated on by Dr. Cushing), in which the hemorrhages had recurred for more than fourteen years, death occurred on the tenth day from rupture of an esophageal varix. In Case XVI. (operated on by Professor Halsted) the patient died of uncontrollable hemorrhage from the large veins passing between the stomach and the spleen. Recurring hematemesis, the most serious event in the disease, and, as I have insisted, usually of splenic origin, is the most important indication for operation.

CONCLUSION. A growing clinical experience should give a sort of miniature picture of the general clinical experience of the profession. Few of us see all the aspects of any disease; few of us recognize all the aspects of the diseases we see; but all of us can try to correlate our own observations with the facts presented by our colleagues, and this is what I have attempted in these papers on splenic anemia. The conclusion to which I have been led by the study of a remarkable group of cases is that—

From among the conditions with which anemia and enlarged spleen are associated, a well-defined disease may be separated conforming to the definition above given, and which may be called chronic splenic anemia.

APPENDIX.[1]

I. *Acute Cases.*

1. Musser (Philadelphia).—Hugh E., aged thirty years; duration fifteen weeks. Diarrhea chief symptom; liver and spleen enlarged. Red blood corpuscles, 890,000; hemoglobin, 20 per cent.; no nucleated red corpuscles; leukocytes average of seven counts, 2400; lowest, 1200 per cubic millimeter.

2. Kelly, A. O. J. (Philadelphia).—W. E. K., female, aged twenty-two years; duration twelve months. Spleen only two fingers' breadth below the costal border. Lowest blood count, 3,070,000 per cubic millimeter; hemoglobin, lowest, 33 per cent.; leukocytes, 6300; nucleated red corpuscles abundant. Death.

3. Wilson, J. C. (Philadelphia).—John V., aged twenty-five years; duration under one year. Spleen three fingers' breadth below the costal border. Red blood corpuscles, 1,650,000 to 4,580,000; hemoglobin, 18 to 65 per cent.; leukocytes, almost always under 4000 per cubic millimeter; no nucleated reds. Yellowish-green tint of skin; marked improvement at date of report.

[1] I am much indebted to my colleagues for the trouble they have taken in sending these reports.

4. Cary (Buffalo).—S., male, aged fifty-nine years; duration eight months. Etiology obscure. Red blood corpuscles, lowest, 1,776,000; hemoglobin, 41 per cent.; leukocytes, 3075; nucleated red corpuscles present. Death. Spleen weighed 1270 grams; liver weighed 2280 grams. No jaundice.

5. Fitz (Boston).—T. B., male, aged twenty-seven years; duration one year. Armenian. Frequent epistaxis; spleen enlarged; liver normal. Red blood corpuscles, 3,652,000 per cubic millimeter; hemoglobin, 65 per cent.; leukocytes, 5800.

6. Fitz (Boston).—T. D., male, aged twenty years; duration one year. Typhoid fever twice; spleen and liver enlarged; jaundice; epistaxis. Red blood corpuscles, 2,500,000; hemoglobin, 40 to 45 per cent.; leukocytes, 20,000.

7. McPhedran (Toronto).—W. W., male, aged thirty-five years; duration several months. Red blood corpuscles, 3,500,000; hemoglobin (?); leukocytes, 7000. Liver slightly enlarged; jaundice well marked; did well on arsenic; relapsed; lost sight of.

8. Edwards, A. R. (Chicago).—Male, aged sixty-five years; duration eleven weeks. Red blood corpuscles, 2,500,000; hemoglobin, 40 per cent.; leukocytes, 5400; nucleated red corpuscles present. Spleen reached half-way to navel; skin lemon tint; repeated (ten or twelve) hemorrhages from the stomach; liver not enlarged; death; no autopsy.

9. Blackader (Montreal).—F. S., male, aged forty-two years; duration six weeks before admission. Malaria fifteen years previously; spleen reached to navel. Red blood corpuscles, 1,106,000; eight days later, 843,336; leukocytes scanty. Liver enlarged; temperature, 100° to 103° F.; diarrhea.

10. Martin, C. F. (Montreal).—Male, aged thirty-nine years; duration of illness five months. After complaining for a time of shortness of breath he had slight hematemesis, and once a large dark (probably bloody) stool. On admission, November 15, 1900, profound anemia; spleen much enlarged, reaching nearly to the navel. Red blood corpuscles, 2,060,000; hemoglobin, 25 per cent.; leukocytes, 2000. Died end of December.

11. Sears (Boston).—A. I., female, aged forty-nine years; duration six months (?). Malaria fifteen years ago; liver enlarged; ascites present. Red blood corpuscles, 3,008,000 to 4,240,000; hemoglobin, 30 to 35 per cent.; leukocytes, 2600 to 3800.

12. Rotch (Boston).—James P., aged four months; duration of illness two months. Spleen reached to middle line and nearly to crest of the ilium; liver 3 cubic millimeters below the costal border. Red blood corpuscles, 2,408,000; hemoglobin, 25 to 30 per cent.; leukocytes, 2800; no nucleated red corpuscles.

II. *Chronic Cases.*

1. Musser (Philadelphia).—J. P., aged twenty-eight years; duration seven years. Spleen very large; liver ½ cubic millimeter below costal margin; diabetes chronic; hemoptysis; epistaxis. Red blood corpuscles, 1,990,000; hemoglobin, lowest, 30 per cent.; leukocytes, 2040 to 6400 per cubic millimeter;

nucleated red corpuscles. Death, acute pneumonia; light yellow tint of skin through the illness. Case reported as Banti's disease by H. A. Hare; case also under J. C. Wilson. Postmortem: hyperplasia in liver; pancreatic sclerosis.

2. Kelly, A. O. J. (Philadelphia).—J. M., male, aged thirty-six years; duration three years. Spleen a hand's breadth below the costal border; liver slightly enlarged; hematemesis a marked feature of the case. Red blood corpuscles, lowest, 2,110,000; hemoglobin, 47 per cent.; leukocytes, 4200. Still under observation.

3. Fitz (Boston).—K. T., male, Armenian, aged twenty-two years; duration of illness three years. Malaria (?); spleen enlarged; liver normal. Red blood corpuscles, 3,920,000; hemoglobin, 55 per cent.; leukocytes, 2900.

4. Fitz (Boston).—Annie H., Armenian, aged thirty years; duration of illness five years. Malaria (?). Red blood corpuscles, 3,693,000; hemoglobin, 53 per cent.; leukocytes, 7800. Liver and spleen enlarged.

5. McPhedran (Toronto).—Female, aged thirty-one years; duration two years. Red blood corpuscles, 4,000,000; hemoglobin, 73 per cent.; leukocytes, 6500. Spleen much enlarged; liver slightly enlarged; moderate jaundice; laparotomy; slight ascites; improvement; death two months later from diphtheria. Diagnosed as Banti's disease.

6. Hun (Albany).—Female, aged thirty years; duration eleven years. Always pale; many attacks of jaundice. Red blood corpuscles, 2,152,000; hemoglobin, 38 per cent.; leukocytes, 14,000. Moderate enlargement of liver. In 1899, pleurisy, with effusion; tubercle bacilli in sputum; spleen enormously enlarged.

7. Cutler (Boston).—Male, aged sixty-five years; good habits; duration six years. Began with vomiting large amount of blood; fainted. Three years later, second attack; four years later, third attack; in July, 1901, fourth attack; in October, fifth attack; in each only a single attack. No nausea or dyspepsia in intervals. Gained weight and strength rapidly. Liver not eularged; no jaundice; spleen enlarged 8 cubic millimeters below the costal border. At time of observation, March 7, 1902, six months after last attack, still pale, but general condition good. Red blood corpuscles, 5,216,000; hemoglobin, 60 per cent.; leukocytes, 6200. Spleen much enlarged.

8. Edes (Boston).—P. H., male, aged nine years; severe; duration four years. In July, 1900, enlarged spleen and ascites. Red blood corpuscles, 3,769,000; leukocytes, 5700. Laparotomy. Ascites returned and then disappeared; copious hematemesis once; no jaundice; liver not enlarged. April, 1902, boy has remained pale; spleen at level of navel. Severe typhoid fever four years before onset of ascites and enlargement of spleen.

9. Peabody (New York).—Camillo E., aged thirty-six years; duration six years. Chills in Italy three months ago; sore on penis two months ago; hematemesis six years ago; six attacks in all—very severe; spleen greatly enlarged. Red blood corpuscles from 1,820,000, on December 24th, to 3,856,000, on February 16th; hemoglobin, 27 to 56 per cent.; leukocytes, 800 to 1400; no nucleated red corpuscles. Liver dulness diminished; no ascites.

10. Herrick (Chicago).—T. S., male, aged twenty-five years; duration more than two years. Typhoid fever three years ago. February 3, 1900, hematemesis, severe; fainted; three subsequent attacks—last severe, in February, 1902. Has grown paler, and has a subicteroid tint. Liver not enlarged; spleen much enlarged, reaching below navel April, 1902. Red blood corpuscles, 2,950,000; hemoglobin, 35 per cent.; leukocytes, 2600; no nucleated red corpuscles.

11. Dock (Ann Arbor).—Male, aged forty-one years; duration sixteen months. No hemorrhages; no jaundice; liver slightly enlarged. Red blood corpuscles, 4,480,000; hemoglobin, 75 per cent.; leukocytes, 5857; a few nucleated red corpuscles.

12. Vickery (Boston).—Fanny S., aged seven years; duration of illness eight years. In 1894 profuse hemorrhage from the stomach; liver not enlarged; spleen much enlarged. Red blood corpuscles, 2,560,000; hemoglobin, 20 per cent.; leukocytes, 650 to 700; no nucleated red corpuscles. In 1899 intense hemorrhage from the stomach; death.

13. Stockton (Buffalo).—W. B., male, aged fifty-two years; duration more than two years. Spleen reached to the navel; liver enlarged; no hemorrhages. Red blood corpuscles, 4,650,000; hemoglobin, 68 per cent.; leukocytes, 13,000. (Case of Dr. Woehnert's.)

14. Stockton (Buffalo).—M. S., male, aged fifty years; duration one year. Spleen very large; liver enlarged. Red blood corpuscles, 2,685,000; hemoglobin, 45 per cent.; leukocytes, 4000. No jaundice or ascites; marked pigmentation of the skin.

15. Stockton (Buffalo).—Male, aged sixty years; duration eighteen months. Spleen greatly enlarged; liver enlarged; marked sallow pigmentation. Red blood corpuscles, 2,900,000; hemoglobin, 55 per cent.; leukocytes, 3900.

16. Atkinson, A. D. (Baltimore).—Male (colored), aged forty-eight years; duration seven years +. No malaria. In 1892, attack of jaundice, with swelling of the abdomen; in 1894, melena; in 1897, a second attack. Enlarged spleen discovered in 1898; ascites. Red blood corpuscles, 4,000,000; hemoglobin, 54 per cent.; leukocytes, 1500. In August, 1899, vomited large amount of blood; liver not enlarged. Autopsy: spleen weighed 2400 grams—chronic hyperplasia; Malpighian bodies not made out; liver was not enlarged and showed no well-defined increase in the connective tissue.

17. Sears, D. (Boston).—Frank D., aged twenty-seven years; duration seven years. Doubtful history of malaria; no hemorrhages; liver enlarged; no jaundice; ascites present. Red blood corpuscles, 1,808,000 to 2,240,000; hemoglobin, 25 to 30 per cent.; leukocytes, 1850 to 3400; myelocytes, 3.5 per cent.

18. Rotch (Boston).—A. S., male, aged twelve years; duration nine years. When conditions had lasted three years: red blood corpuscles, 2,412,000; hemoglobin, 18 per cent.; leukocytes, 36,000; no nucleated red corpuscles. Liver enlarged; spleen extended below the navel. After condition had lasted nine years: red blood corpuscles, 1,733,000; hemoglobin, 30 per cent.; leukocytes, 6000. Liver still enlarged; skin and conjunctivæ stained, but no bile in urine; spleen extended into the pelvis.

19. Stewart, D. D. (Philadelphia).—Mrs. A., aged thirty years; duration doubtful, probably some years. Has had peculiar yellow hue since childhood. Spleen greatly enlarged; no enlargement of liver; no jaundice. Red blood corpuscles, 2,684,000; hemoglobin, 58 per cent.; leukocytes, 6700. Has had epistaxis.

20. Cabot, R. C. (Boston).—N., female, aged thirteen years; duration (?). Ascites; hematemesis, caused death; melena; liver not enlarged. Red blood corpuscles, 4,280,000; hemoglobin, 42 per cent.; leukocytes, 1300 to 2100.

21. Cabot, R. C. (Boston).—D., female, aged twenty-three years; duration ten years. Liver not enlarged; hematemesis at intervals for ten years; died of hemorrhage. Red blood corpuscles, 1,656,000 to 4,240,000; hemoglobin, 18 to 60 per cent.; leukocytes, 1300 to 2300.

22. Cabot, R. C. (Boston).—A., male, aged twenty-four years; duration (?). Jaundice; liver enlarged; no hemorrhages. Red blood corpuscles, 4,620,000; hemoglobin, 48 per cent.; leukocytes, 6400.

23. Cabot, R. C. (Boston).—N., male, aged thirty-two years; duration (?). Red blood corpuscles, 4,684,000; hemoglobin, 55 per cent.; leukocytes, 9000; 18 normoblasts per cubic millimeter.

24. Cabot, R. C. (Boston).—W., female, aged fifty-three years; duration (?). Red blood corpuscles, 4,790,000; hemoglobin, 65 per cent.; leukocytes, 4800.

25. Cabot, R. C. (Boston).—I. H., male, aged thirty-five years; Armenian; duration (?). Red blood corpuscles, 3,484,000; hemoglobin, 45 per cent.; leukocytes, 4500.

26. Cabot, R. C. (Boston).—T., male, aged twenty-seven years; duration unknown. Red blood corpuscles, 3,652,000; hemoglobin, 65 per cent.; leukocytes, 5800.

III. *Simple Splenomegaly.*

Herrick (Chicago).—Felix G., aged twenty-five years; duration many months, probably two to five years. Spleen greatly enlarged; liver normal. Red blood corpuscles, 5,120,000; hemoglobin, 80 per cent.; leukocytes, 5000. Has not been well for five years.

Blackader and C. F. Martin (Montreal).—Male, aged twenty-one years. At eighteen had an attack of jaundice; nothing abnormal in abdomen. In January, 1901, by an accident, in which he was struck in the abdomen, he was knocked breathless; on recovery vomited a dark material. Afterward the spleen was found to be enlarged, and it has gradually increased in size to date, and now crosses the middle line. Red blood corpuscles, 4,710,000; hemoglobin, 90 per cent.; leukocytes, 5000.

IV. *Other Diseases.*

Cary (Buffalo).—V. B., aged forty years. Hemorrhages, melena, and epistaxis. Red blood corpuscles, 4,600,000; hemoglobin, 6 per cent.; leukocytes, 3120. Spleen enlarged. Doubtful, during life, of splenic anemia. Postmortem: cirrhosis of liver. Spleen weighed 730 grams; liver, 1860 grams.

Ewing (New York).—F., aged thirty-two years; duration four years. Spleen very large, 1470 grams. Red blood corpuscles, 2,908,000; hemoglobin, 45 per cent.; leukocytes, 3300. Liver enlarged; ascites. Postmortem: large round-celled sarcoma of spleen (epithélome primitive); gummata of spleen; diffuse cirrhosis of liver. (Case to be published by Dr. C. W. Field.)

In Cary's case the picture during life suggested splenic anemia, but the postmortem showed alcoholic cirrhosis, with enlarged spleen. In Ewing's case there was round-celled sarcoma of the spleen, with gummata, and also diffuse cirrhosis of the liver. It is interesting to note the similarity of the blood condition to that in cirrhotic splenic anemia. It is quite possible that when the full report is published this case will prove to be similar to those of Bovaird and others.

V. *Cases Difficult to Classify.*

I. Musser.—J. H., aged forty-five years; duration four years. Syphilis. In latter part of 1898 and 1899 jaundice, with enlargement of spleen and liver; hemorrhages of stomach and bowel. Lowest blood count, 3,200,000 per cubic millimeter; hemoglobin, lowest, 65 per cent.; no leukocytosis. He had cerebral syphilis.

II. Greene.—Mrs. L. H., aged twenty-one years; duration four years—followed typhoid fever. Spleen five inches below the costal margin; liver not enlarged; tuberculous history; has had cough and expectoration; flatness at both apices. Red blood corpuscles, 2,500,000; hemoglobin, 45 per cent.; leukocytes, 10,000.

III. Sears.—J. W., female, aged forty-six years; duration twelve years (?). Biliary colic for twelve years; no malaria; no syphilis; liver much enlarged; spleen extends to ilium; no hemorrhages; jaundice present; no ascites. Red blood corpuscles, 3,496,000 to 4,308,000; hemoglobin, 60 per cent.; leukocytes, 1400 to 5800.

In I. the possibility of syphilis of the liver has to be considered; in II. the complication of tuberculosis makes one doubtful; while in III. the long duration of attacks of colic make it possible that the whole trouble is pressure on the liver, though it is rare to see, in cirrhosis from any cause, a spleen that reaches to the ilium.

DISCUSSION.

DR. MUSSER: I handed to Dr. Osler to incorporate in his paper the clinical histories of the cases which I have had under my care to which the term Banti's disease might be applied. I am not prepared to dignify the symptom-group with a new name, as splenic anemia or Banti's disease. It is not necessary, and perhaps not correct, to invoke an affection of the spleen as causal of the symptoms. Especially is this so, as in nearly all of the cases reported cirrhosis of the liver is present. Now, why can we not invoke the other end of the portal circulation to explain the symptoms? I recognize the leukopenia, the ascites, the hepatic cirrhosis with enlargement of the spleen as a congerie of symptoms which make up the clinical picture Dr. Osler draws. But is it not also the picture of hepatic cirrhosis? I have recently studied a series of cases of cirrhosis of the liver in which the same blood picture obtains. Who could say positively, from the light of our autopsy experiences, which often show cirrhosis when not expected, although carefully looked for during life, that with so-called primary splenic enlargement there is an absence of hepatic cirrhosis? It is not possible to exclude the liver process. Moreover, my reading does not enable me to distinguish between the histologic appearances of the spleen in so-called Banti's disease and those of chronic splenitis from other causes.

For these reasons, therefore, I am not prepared at present to take position with Dr. Osler without further and more positive proof, for the question is still open. I submit, however, that for the reasons I have mentioned we are warranted to the same degree in assuming that the symptom-group in question is due to cirrhosis of the liver.

DR. BILLINGS: It seems to me that this Association could well take this method of discussing the various subjects that come before us with a great deal of value to the medical world at large. We should thank Dr. Osler for the suggestion, and though it may not be well to prepare symposiums exactly, we might study other conditions conjointly.

I have never seen but two cases that I recognized as belonging to this group, and those I reported to Dr. Osler. In one of these there was distinct decrease in the size of the spleen following a severe hemorrhage, and at the same time the blood count and the amount of hemoglobin went down.

DR. CABOT: I would like to indorse what Dr. Billings has said about the value of the method by which Dr. Osler has had us all work together on this subject. I wish he would in the same way propose a topic each year.

I have put together eight cases that follow the type presented by Dr. Osler. Seven of them have never been reported before, and the eighth was reported by Dr. Warren in connection with the report of the splenectomy which he had performed. These cases all occurred in adults, all had enlargement of the spleen, in no case were the lymphatic glands enlarged, and all had more

or less anemia without obvious cause. Three had profuse vomiting of blood, in two there was enlargement of the liver, and one had ascites as well. There was no pigmentation of the skin in any case.

Besides these eight cases there are seven others which I might speak of and which might have been included had I not kept so closely to the line laid down. Two were excluded because the patients were Armenians, most of whom, as I see them, have enlargement of the spleen. Two were excluded because of the history of having had malaria. Two had increased red count, with enlargement of the spleen. I have no autopsy to report, a fatal objection to laying any stress whatever upon my cases.

In the case operated upon by Dr. Warren the spleen was that of a chronic hyperplasia, without any significant changes.

I can see no good reason for putting these cases together in a separate group other than the request of Dr. Osler, which is always sufficient reason in itself. The blood examination, I should say, was not characteristic. The feature upon which Dr. Osler has insisted, a relatively low hemoglobin, is of no significance, because we see it in other conditions, and the low white count does not render this a peculiar variety of anemia. There seems to be no first-rate reason for using the term splenic anemia. There are many cases of secondary anemia of unknown cause, and many cases of enlargement of the spleen of unknown cause, so that it seems to me that in some cases it may be a pure coincidence that we meet the two together. Others may have had malaria despite their own statement to the contrary; still others may have been hepatic cirrhosis. I regret that the term "splenic anemia" should receive the sanction of Dr. Osler, for I do not believe we are justified in using it.

DR. STENGEL: As I did not hear the paper read I cannot very well discuss it, but I wish to report some cases that have come under my observation, and that seem to me to belong in the group that Dr. Osler has taken up for discussion.

The first of these cases was undoubtedly one of the class which has been described by Banti. The patient was a man over fifty years old. He had been in the French army, and had lived for a time in Mexico. There was an uncertain history of dysentery, but he never suffered with malaria as far as I could learn. The patient was a small-sized man. His spleen and liver were both enlarged, the former especially; the fingers were markedly clubbed; there was a peculiar disorder of pigmentation of the skin; more or less symmetrical areas of vitiligo or leukodermia were scattered over the body and extremities, and the skin between these areas was seemingly darker than normal. His blood count was peculiar in the very small number of leukocytes; the red corpuscles numbered from 60 to 80 per cent. of the normal, and the hemoglobin was somewhat disproportionately reduced. The leukocytes averaged between 3000 and 4000, and in a series of complications that occurred during the two years the patient was under observation, including pneumonia, orchitis, cellulitis, etc., the leuko-

cyte count never exceeded 6000. The differential count never showed any striking variation from the normal. The patient had almost continuous diarrhea; he finally died from exhaustion.

The autopsy showed a large spleen, with increase of fibrous trabecular tissue, giving the substance a peculiarly firm character. There were small hemorrhages in various situations in the substance of the spleen and a deposition of pigment about them. There was no marked hyperplasia of the splenic pulp or Malpighian bodies. The liver was smaller than the normal, and was distinctly cirrhotic. No abnormalities were discovered in the lymphatic glands and no decided change in the bone-marrow, though it was somewhat red. The size of the liver had undoubtedly diminished greatly during the last few months of life. The organ was very large when he first came under observation, two years before his death.

A second case, now under my observation, is of very similar character. The patient, an Italian, is stunted in growth and has clubbed fingers and a deeply pigmented skin, the latter being strikingly darker than that of his Italian friends. He came from a malarial region in Italy, and he has suffered with malaria. He has been in this country ten years, during which time he has suffered no malarial attacks. He has marked enlargement of the spleen and slight diminution in the size of the liver, as evidenced by percussion. Like the other patient, he has had a number of complications, including a recent severe inflammation of the gums and cheek, with high fever and sweats. He has suffered with a form of diarrhea characterized by the discharge of more or less blood-streaked stools. Recently he had a more pronounced hemorrhage from the bowel. The blood count is about the same as in the other case.

In these two cases there was a close similarity of symptoms in these particulars: the patients were stunted in growth, had clubbed fingers and alteration in the pigmentation of the skin; the course of the disease was chronic and progressive; the enlargement of the spleen was decided and out of proportion to the cirrhosis of the liver, if that bears any relation to it at all. There have been gastrointestinal symptoms and a chlorotic type of anemia, especially characterized by pronounced leukopenia. In neither of the cases was there ascites or the marked gastrointestinal hemorrhages that have been described in some instances of splenic anemia.

A third case under my observation came to autopsy a year or more ago. Some clinicians would exclude this case from the category of splenic anemia because it occurred in a child. I did not hear the paper, and, therefore, do not know Dr. Osler's views in this matter at the present time. In his previous publication he has opposed the inclusion of cases of anemia with splenic enlargement occurring in childhood among the cases of splenic anemia. This position is justified with regard to many, and perhaps most of the cases of enlargement of the spleen in childhood; but there are some like the one that was under my care which seemed to me properly to belong in this group. The case occurred in a child of five, and showed, in addition to the splenic enlargement, enlargement of the liver, progressive chlorotic anemia with

slight leukocytosis, some emaciation, and, finally, death occurred from exhaustion. At the autopsy there was found a recent miliary tuberculosis, the point of origin being undiscoverable. The spleen presented much the same character as those found in the first case, and it is because of the peculiar character of the spleen that I would include it with the other two cases.

While reporting these cases in connection with the discussion of splenic anemia, I must confess that I do not see that a distinct form of disease has been separated, though for convenience of clinical classification we may include some peculiar forms of disease with great splenic enlargement under that head. The basis of classification must eventually be the pathologic findings. These have certainly indicated a secondary form of splenic disease, excepting in the few instances of primary splenomegaly like that of Bruhl and Bovaird and the rare cases of Hodgkin's disease involving the spleen. The great majority of cases have shown secondary splenic hypertrophy, and it is evident that a variety of conditions might act as the primary cause of such splenic enlargement.

THE PRESIDENT: I am sure the Society would be very happy to have Dr. Stiles take part in the discussion.

DR. STILES: In cattle we frequently find tremendously enlarged spleens, especially in the outbreaks of disease in the cattle of Texas. My postmortem examinations there were usually made when the temperature was 104° or higher, and I could not make blood examinations; but I traced the cause of the outbreak of the infection to parasites, particularly the encysted strongile in the wall of the stomach. The fourth stomach of the animals presented a condition very similar to that found in the muscles of man in severe cases of trichinosis. I have no suggestion to make in connection with this discussion, but it struck me that no one has mentioned any intestinal examinations. We have in man a strongile that lives in the stomach and that has been reported only twice, once from Japan and once from Egypt. I might suggest the advisability of looking for these intestinal parasites in such cases of anemia, for I am convinced that we have many cases of anemia in this country due to stronguloides which is overlooked. During the past week I have been able to demonstrate my position absolutely by finding a case with a parasite which I have named Uncinaria Americanus, because it differs in some respects from the duodenalis, which may be called the foreign species. It was found in a case of anemia with enlarged spleen.

DR. THOMSON: In answer to Dr. Osler's request I prepared a statement of four cases, but on looking them over I can see that they illustrate what Dr. Osler has just described as the motley group of cases. I should say that in my own experience these cases of enlarged spleen which end fatally have had autopsies extremely varied in their results. If the term splenic anemia is to apply in itself to some primary disease of that organ I should object to

it. In the case of the other lymphatic glands, their removal is fatal; they are necessary to life. But in the case of the spleen we have an organ which can be removed with impunity. If, therefore, its functions are of such secondary importance that they can easily be made up for by other organs, why should we expect a primary disease of the spleen ever to amount to much? On the other hand, considering that there is scarcely any severe disease occurring without the spleen becoming secondarily involved, and if the clinical features accompanying certain forms of enlargement are so definite that we can always determine it, I should say that I would accept the adjective splenic as descriptive of anemia.

DR. KINNICUTT: I would simply ask one question apropos of Dr. Stengel's remark, Whether there is any good reason for excluding the splenic anemias of children?

DR. OSLER: Nothing could vindicate more thoroughly the necessity for bringing this subject up than the character of this discussion. I do not know whether the confusion which existed before is more or less confounded. I do feel, however, that we will study our cases of anemia a little more closely hereafter. I did not offer the name "splenic anemia" myself, far from it; I only used it because there is nothing else at hand, and so far as I know it is the only one to apply to the group of cases which I have tried to cull out from the motley series of cases of anemia with big spleen. Concerning the relation to cirrhosis, there is no question that such cases as I have described with hematemesis and ascites may exist without any changes in the liver. Later in a number of cases the liver becomes sclerotic, as described by Banti, and when we speak of Banti's disease it should be of the terminal stage, with cirrhosis of the liver, jaundice, and ascites.

AN ESTIMATE OF THE AMOUNT OF TOXIN IN THE BLOOD OF HORSES INFECTED WITH TETANUS.

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AND
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THOSE who read the report of our investigation into the cause of the outbreak of tetanus in St. Louis last autumn will perhaps recall that this outbreak was shown to be due to the use of diphtheria antitoxin which contained tetanus toxin. The antitoxin used in these cases was obtained from a horse that exhibited symptoms of tetanus two days after the blood was drawn. We were able to demonstrate without difficulty the presence of a considerable amount of toxin in this serum, but we could find no evidence in the literature that this had been done under similar circumstances before. Buschettini[1] found tetanus toxin in the blood, liver, spleen, and kidney in the disease of a human being. Bolton[2] found it in the spinal cord in a human being. In human beings and in animals it is sometimes found and sometimes missed in the various tissues and organs after symptoms have developed and after death from tetanus.[3] The facts seem to show that the toxin in some cases, whether it is injected into the blood or whether it develops in the tissues from infection, disappears from the blood and becomes combined with the other tissues; at any rate, it is not to be detected free in the blood unless the amount of toxin present is more than sufficient to satisfy the combining affinity of the tissues. In other cases, on the contrary, none but the nerve tissue takes up the toxin, and the latter is found in the blood even where small amounts are present.[4] In guinea-pigs most of the toxin remains circulating in the blood when it is injected into the circulation, the nerve tissue alone seems to have affinity for the toxin; in rabbits, on the other hand, the toxin combines with the tissues and disappears from the

blood, at least as free toxin, in eighteen hours,[5] even where many times more than the fatal dose is injected. We found no free toxin in the blood, spinal fluid, or other tissues in the children that had received subcutaneous injections of the toxin in the cases already referred to in St. Louis. But it will be noted that all these observations were made either after the symptoms had developed in cases of infection, or after the injection of toxin, none of them during the period of incubation after infection, as was the case with the horse in which toxin was found in the blood, in our report already alluded to. In order to supplement the observations made in this case we have tested the blood from several other horses infected with tetanus.

The blood from four horses in all has been tested: three were inoculated intentionally; one was a case of accidental infection. Two of the horses were inoculated with earth that contained the tetanus organism, as shown by previous inoculation of smaller animals; one was inoculated with a culture. The blood in the case of accidental infection was drawn thirty-six hours after the first symptoms developed.

The first horse was inoculated with a small amount, perhaps 0.5 c.c. of earth that had been shown to contain the tetanus organism by the inoculation of a rat and a guinea-pig. It is very remarkable that the horse showed no signs of tetanus from this inoculation, and the blood drawn at intervals of twenty-four hours had no toxic properties. Twenty-one days after the first attempted infection the horse was again inoculated with a second portion of the same earth, but a much larger amount was used. The earth was suspended in water, strained through a cheese cloth, and injected deep into the tissues of the shoulder with a large antitoxin syringe. The canula from the syringe was accidentally broken off and remained in the tissues. The animal appeared sick on the afternoon of the sixth day after inoculation, and died in the night between the sixth and seventh days. There were no characteristic symptoms of tetanus in this case, but the blood obtained four days before death and subsequently showed the presence of tetanus toxin. The blood drawn two days before death contained the greatest amount of toxin; that obtained four days before death the least amount; that obtained on the fifth and sixth days before death showed no toxin. The exact fatal dose was not ascertained, but, as will be seen from the accompanying table, the amount for rats was about 3 c.c. in the weakest serum, and somewhat less for the other specimens. The

minimum dose for guinea-pigs varied in the same way, from about 1.5 to 2 c.c.

HORSE No. 1.—Inoculated with tetanus earth January 23, 1902, with no result. Reinoculated with a large amount of the same earth February 7, 1902. Died February 13, 1902.

Serum from days after inoculation.	Guinea-pigs.				Rats.		
	Weight in grams.	Amount of serum injected.	Time of development of first symptoms.	Time of death after inoculation.	Amount of serum injected.	Time of development of first symptoms.	Time of death after inoculation.
1	230	1 c.c.	0	0	3 c.c.	0	0
2	245	1 "	0	0	3 "	0	0
3	222	1 "	0	0	3 "	0	0
3	...	.....	...	...	3 "	4 days.	6 days.
4	246	1 c.c.	2 days.	0	3 "	2 "	5 "
4	?	0.5 c.c.	3 "	0			
6	242	0.5 "	3 "	0	3 c.c.	3 "	5 "

The second horse was inoculated with a splinter smeared with earth rubbed up with water. This inoculation was not followed by any result, the horse exhibited no symptoms of disease, and the blood failed to show any toxin, a result that corresponded with the first attempt at inoculating the first horse. Twenty-nine days after this unsuccessful attempt the horse was again inoculated, this time with an agar culture isolated from earth. The culture was first heated for half an hour at 60° C. in order to destroy the toxin. Symptoms of tetanus, consisting of stiffness in the legs and neck, appeared in this case on the thirteenth day after inoculation with the culture, trismus came on one day later, and all symptoms progressed steadily until the death of the animal, which took place on the sixteenth day after inoculation. The serum from the blood of this animal contained no toxin until the eighth day before death, the fifth before any symptoms were observable. The toxin gradually increased in amount till the third day before death, which was the date of the first symptoms. From this time on the toxin rather suddenly decreased in amount, and disappeared entirely on the day of death; at least the serum drawn an hour before death produced no symptoms in a mouse inoculated with 1 c.c.

HORSE No. 2. — Inoculated with a splinter smeared with tetanus earth, February 20, 1902, with no result. Reinoculated with an agar culture March 21, 1902. First symptoms of tetanus April 3, 1902. Died April 8, 1902.

Serum from days after inoculation.	Mice.			
	Weight in gms.	Amount of serum injected.	Time of development of first symptoms.	Time of death after inoculation.
1	(The weight of the mice varied between 13 and 15 grams.)			
2				
3	.....	1 c.c.	0	0
4	.....	1 "	0	0
5	.....	1 "	0	0
5	.....	2 "	0	0
6	.....	2 "	0	0
7	....	2 "	0	0
8	.....	1.5 "	5 days.	Recovered.
9	.....	1 "	4 "	"
10	.....	0.5 "	3 "	7 days.
11	.....	0.25 "	2 "	6 "
12	.....	0.2 "	1 day.	5 "
13	.....	0.1 "	1 "	5 "
14	.....	0.1 "	2 days.	8 "
15	.....	0.25 "	3 "	Recovered.
16	.....	1 "	0	0

The third horse was inoculated with 1 or 2 c.c. of tetanus earth, a part of the same earth from which the culture was obtained in the foregoing case, but as yet no symptoms have developed, twenty-seven days after the inoculation. We have purposely refrained from inoculating this horse again in order to see whether tetanus will eventually develop. The wound was on the side of the spine back of the shoulder, and there was a large abscess formed, which discharged a large amount of foul-smelling pus. The earth was introduced about three inches under the skin in a pocket made with a pair of long forceps.

The fourth horse was one that had accidental infection, and only one specimen of blood was secured. As already stated, this was obtained thirty-six hours after the appearance of the first symptoms,

about one day before death. It contained a small amount of toxin (3 c.c.), produced marked symptoms, but not death, in a guinea-pig; 0.7 c.c. produced fatal tetanus in a mouse.

From the above results it is apparent that the toxin makes its appearance in the blood of the horse several days before any symptoms of tetanus are to be observed, and that it gradually increases until about two days before the symptoms become noticeable; after this it rather suddenly diminishes, and even disappears in some cases. Tests are now under way to see whether there is any antitoxin in the serum, which showed no toxin, taken an hour before the death of horse No. 2. The amount of toxin varies considerably in different cases. The amount present in the serum from the diphtheria antitoxin horse tested last autumn was sufficient to kill a guinea-pig in the dose of 0.1 c.c., and in this case the serum was drawn at a time when the maximum amount of toxin was probably present, about two days before symptoms developed. In horse No. 1 the minimum fatal dose of toxin in the blood at a similar period was more than 1 c.c. In horse No. 2 the minimum fatal dose for a mouse was about 0.1 c.c., or somewhat less. This, reckoned out for a guinea-pig, is approximately 0.21 gm., since, according to Behring's[6] calculation, the guinea-pig is five times more susceptible than the mouse, weight for weight, and, according to Knorr,[7] the proportion is about the same. In horse No. 4, according to the same calculation, the minimum fatal dose for a guinea-pig would be about 1.5 c.c., but in this case the serum was not taken at the time of the maximum strength. In our former paper we calculated that susceptibility of human beings is about 0.85 as compared with a guinea-pig; consequently the fatal dose for human beings in the four horses would be 10, 100, 21, and 70 c.c. respectively.

The difficulty of producing tetanus in horses by inoculation with earth is surprising when it is considered how susceptible the horse is to the toxin of tetanus and the frequency of infection from accidental wounds. As will appear from what has been said above, we succeeded only once in reducing tetanus by inoculation with earth which caused the disease promptly in guinea-pigs, rats, and mice, and we succeeded this time only by inoculating a second time with a large amount of earth. We are unable to offer a satisfactory explanation of this.

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DISCUSSION.

DR. ABBOTT: I had an experience last winter that bears upon this question. There was sent to my laboratory the blood of a child something less than twenty-four hours after its death from tetanus. The blood was injected beneath the skin of two white mice in 0.5 c.c. doses, but in neither instance did tetanus convulsions develop. We concluded that the toxin that had caused the death of the child had combined with the tissues of the central system.

DR. MELTZER: I would like to ask Dr. Bolton whether he has tested the blood of the horse for tetanolysins. As you know, Ehrlich, and especially Marsden, have found that the toxin of the tetanus contains two different constituents—tetanospasmin and tetanolysin. The tetanospasmin does not remain in the blood long, but becomes fixed in the nervous system, while the tetanolysin remains in the blood for a long time. Now, if some of the horses in which Dr. Bolton has injected tetanus bacilli subcutaneously have not shown any tetanic symptoms, this may be due to either of two causes: either the tetanospasmin was rapidly fixed and neutralized by the antitoxic power of the nervous system, or the toxins were not absorbed at all from the subcutaneous tissue. In either case no tetanospasmin would be found in the blood, but if the tetanus toxin had been absorbed from the subcutaneous tissue the blood would have contained tetanolysin. Therefore, I think that the examination of the blood for tetanolysin would help to establish whether in those cases in which the injection has not brought out any tetanic symptoms the tetanus toxin was absorbed or not.

THE HEALING OF ULCERATIVE ENDOCARDITIS.

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Since Bouillaud's time (1837) two types of acute endocarditis have been recognized: the vegetative or benignant, and the ulcerative or malignant; but neither anatomically nor clinically can a sharp line of demarcation be drawn separating the one group from the other. Both are by common consent regarded as infectious in origin, though the part that may be played by toxins is not clearly defined. There are striking differences between the anatomical appearance of these forms: the vegetative, with its little innocent looking, warty fringe paralleling the edges of the valves; the ulcerative, with massive excrescences, crater-like excavations, perforated valves, and purulent coating. And the contrast is as striking clinically between the extremes of a faint cardiac murmur—little or no disturbance in the cardiac force and rhythm, and insignificant constitutional disturbances of the benignant—and the fulminant malignant type, with its chills, irregular fever, prostration, typhoid state, embolic phenomena, and rapid death.

But between these extremes are to be found all degrees of anatomic alteration, and, clinically, the one form shades imperceptibly into the other, so that one must often be content to speak of an acute infectious endocarditis or of an acute endocarditis, with mild or severe manifestations as the case may be. If it were possible to recognize the micro-organism that was at fault in a given case, it would be a more scientific classification to speak of a pneumococcic, a streptococcic, a gonococcic endocarditis, etc. Yet until this is possible it is wise, from the standpoint of prognosis and therapy, to recognize two types of the disease in the same manner that we often speak of scarlet fever as extremely light in one case or malignant in another, though believing the disease in the two cases to be primarily of the same nature, but modified by greater virulence or number of

organisms, by lessened resisting power on the part of the patient, or by failure to eliminate toxins. So, while it is well to preserve the expressions ulcerative or malignant in connection with endocarditis, it must be remembered that the terms are used rather loosely in an anatomic sense, and also to a certain extent in a clinical sense.

Clinically, by ulcerative or malignant endocarditis is commonly meant an acute endocarditis accompanied by a fairly uniform complexus of symptoms, among which may be mentioned irregular fever, with chills, embolic phenomena, petechiæ, bacteria in the blood, pronounced constitutional disturbance in the shape of symptoms of the typhoid state—delirium, subsultus, sordes—progressive anemia, etc. The usual termination of these cases is death within a few weeks, or in one form after many months, and the anatomic finding is the mycotic, destructive lesion of the valves. The prognosis is, therefore, bad or fatal in the malignant endocarditis. Or, to put the statement in another way, it is often said that if the patient recovers, the case was one of the benignant or vegetative form; if he dies, it was malignant or ulcerative. This is making our disease fit a definition, always a pernicious practice. Perhaps argument to prove the possibility of occasional healing in this severer form is unnecessary, at least before this audience. Yet the impression regarding the fatality of this variety is so prevalent that if a case diagnosed as ulcerative endocarditis recovers, as a rule there is declared to have been a mistake in diagnosis, and treatment in these cases is considered absolutely futile. It may not be amiss, therefore, briefly to call attention to certain facts that indicate the possibility of recovery.

One has a right to question whether an acute endocarditis, with irregular fever, chills, petechial spots, and bacteria in the blood is of necessity fatal. We may question on the ground of *a priori* reasoning, of clinical observations, and of postmortem findings.

Some severe cases of septicemia, in man as in the lower animals, recover. Puerperal sepsis, though virulent, is not necessarily fatal. Pneumonia is often accompanied by bacteriemia, by metapneumonic localization, and yet recovery may follow. While one realizes the added seriousness that is due to the establishment of a focus of microbic multiplication and toxin formation in the very center of the vascular system, from which center organisms and their products are freely swept out into the circulation and disseminated to the most

distant parts of the body; and while one understands fully the gravity of the mechanical interference with the valvular and muscular mechanism of the heart that often accompanies an acute endocarditis, one must still feel that it is possible, even here, for the body to resist, for the inflammatory process to subside, and for local healing and constitutional recovery to ensue.

This view is borne out by clinical observation. There are records in the literature where competent observers have had cases with the typical symptoms of acute endocarditis of the so-called ulcerative type—chills, irregular pyemic fever, petechiæ, visceral embolic phenomena in the blood, and recovery has followed, with the exception, perhaps, of some mechanical lesion due to the scarring of the valves. These cases are exceptional, to be sure; this complexus of symptoms usually means death; but recovery may occur if these observations are correct. It is easy to pick flaws in many of these histories. But there is a value to the impression made by a given case upon a skilled clinician, and his estimate of a case when he shows capacity to observe carefully and to weigh evidence critically should be given much weight, even though the crucial tests may be lacking and though his results are opposed to generally accepted opinion.

There is no pretence that this is a complete list of all cases reported as recoveries from malignant endocarditis. More extended search will reveal others, but enough are here given to call attention to the fact that recovery is regarded by many as occasionally occurring.

A. E. Roussel (*Medical Record*, 1901, vol. lix.). A woman, following a miscarriage, had a foul uterine discharge, then continued fever, with occasional spells of subnormal temperature, chilliness, sweats, pains in various parts of the body, great emaciation. The heart became tumultuous; its area of dulness increased; systolic, apical, and basic murmurs appeared; the pulse was often irregular and as high as 148; there were a dull pain and feeling of oppression in the region of the heart. The red corpuscles were reduced to 3,000,000, hemoglobin was 35 per cent.; leukocytes 26,000; streptococci were present in the blood, and several subcutaneous abscesses containing streptococci formed. After twelve weeks the patient recovered. Examination six months later showed a gain of twenty-five pounds in weight, freedom from fever, but there were cardiac hypertrophy and persistence of endocardial murmurs. Here was a case of puerperal sepsis with valvular localization, and symptoms commonly regarded as those of the malignant or ulcerative variety, yet recovery ensued.

Dreschfeld (*Allbutt's System*, i. p. 632) tells of a patient in whom, after a

severe bodily strain, signs of aortic leakage were found, evidently a rupture of the aortic valves. Some time later the patient had symptoms of malignant endocarditis, repeated chills, intermittent and high temperature (105°), and eventually embolism of the posterior tibial artery. The febrile symptoms subsided after a time, the patient regained his strength, and the diastolic murmur of the aortic regurgitation remained. In this case the valves damaged by rupture furnished the suitable nidus—the locus minoris resistentiæ—for the development of micro-organisms that in some way gained entrance to the blood.

Sansom (*Practitioner*, vol. xl. p. 21) treated a woman for what he believed was acute ulcerative endocarditis affecting the mitral and aortic valves. She recovered, with the signs, however, of mitral and aortic regurgitation. Ten months later she suffered from symptoms similar to those he had observed in her first attack. She died, and the autopsy revealed ulcerative endocarditis, with temporary recovery. Sansom regards the first attack as one of ulcerative endocarditis.

Rosenbach (*Die Krankheiten des Herzens*, Vienna, 1897, p. 175) says that mycotic or malignant endocarditis, like any other form of sepsis, is capable, though, unfortunately, only rarely, of completely healing, often in an entirely unexpected manner. He cites the case of a child that, with joint and cardiac affections, had complete recovery so far as the joint and heart were concerned, but lost the eye through an ophthalmia, an evidence of the malignant, microbic nature of the trouble.

Fraentzel (O. Fraentzel, *Die Krankheiten des Herzens*, Berlin, 1891, vol. ii. p. 36) saw malignant endocarditis develop in two cases of severe uterine phlebitis. The women were both living, the one twenty-two years, the other eleven years, after the occurrence of the endocarditis, though with slight valvular defects. He also saw two cases of uncomplicated primary malignant endocarditis in which the chills gradually ceased, and there finally remained nothing but a vitium cordis. One of these patients died three years later of the mechanical effects of regurgitation.

N. S. Davis, Jr. (*Journal of the American Medical Association*, 1901, vol. xxxvi., No. 1, p. 14, "Ulcerative Endocarditis, with Recovery"). Male, aged twenty-five years, non-alcoholic. Headache and dyspeptic symptoms, with some dyspnea on exertion for about a year. Physical examination negative on admission to the hospital. For one week temperature and pulse normal. Then temperature like typhoid, endocardial murmur, irregular chills, phlebitis of vein in leg, anemia, emaciation; gradual recovery. Créde ointment used. Malaria excluded by examination of blood. No rose spots of typhoid, no Widal, no tympany. Regarded by Dr. Davis as ulcerative endocarditis, with recovery.

T. L. Coley (*Medical Record*, 1897, vol. li. p. 6, "Malignant Endopericarditis, with Recovery"). Male, aged twenty-six years, rheumatism at nine years. Never quite so well after, suffering somewhat from dyspnea and palpitation. For six weeks furuncles, a possible source of the infective trouble. Had

precordial distress, syncope, with rigors; serous diarrhea; became weak and emaciated. The heart showed great enlargement and typical signs of aortic regurgitation, including Corrigan pulse; also a double murmur at the apex and accentuated pulmonic tone. A pericardial friction was heard. Palpable spleen. Repeated chills, fever, and drenching sweats; morning temperature subnormal. Irritable stomach; marked secondary anemia; reds, 2,100,000; hemoglobin, 26 per cent.; whites, 7200. No organisms detected in blood (four examinations). Urine albuminous, twice with blood; epithelial casts. At times muttering delirium. In bed from November 15, 1895, to May 20, 1896. In August, 1896, had regained weight and was able to do light work. Physical signs of mitral and aortic lesions.

Warren Coleman (*Philadelphia Medical Journal*, 1900, vol. vi. p 1193, "Infective Endocarditis following Vaccination, with Recovery"). Female, aged twenty-three years, in previous good health. Vaccination two months before, followed by extensive cellulitis and axillary adenitis. Weakness, fever, pains about joints, and in three days areas like erythema nodosum. Chills and sweats on many occasions. Septic appearance, anemia, continued fever up to 103°. Heart showed mitral murmur with accentuated pulmonic. Right heart increased in size during illness. Aortic roughening and murmur developed. Pulse grew intermittent and irregular; vessels of neck pulsated visibly. In six weeks improvement. Examination of chest two and a half years after showed no murmurs and very little increase in size. Previous to the fever the heart had been examined and found normal.

Edmund Cantley (*Lancet*, 1891, vol. i. p. 1375, "A Case of Recovery from Acute Infective Endocarditis"). Male, aged twenty-four years; good previous history. For three weeks nausea, weakness, slight chills and fever, headache, pains, especially in joints. Spleen palpable. Rigors at irregular intervals, sometimes two in a day. Temperature high. A blowing systolic murmur at the apex, and a more marked systolic murmur at the lower end of the sternum. After a prolonged course, with numerous chills, fever, and sweating, with weakness and emaciation, there was gradual improvement, and he was discharged in good condition eight months from the commencement of his illness. The murmur at the apex finally disappeared, but the one to the left of the lower end of the sternum remained.

J. W. Washburne (*Lancet*, 1897, vol. ii. p. 707, "A Case of Ulcerative Endocarditis Successfully Treated with Antistreptococcic Serum"). Female, aged twenty years. Uneventful personal history. Pains in joints, headache, shivering. Heart, lungs, and urine normal, and no external evidence of disease of the joints. Irregular, intermittent pyrexia. Temperature at times normal, at times 102°–105°. Rigors and sweats. Slight leukocytosis and reduction in hemoglobin and red corpuscles. A distinct diastolic bruit developed, best heard on the left side of the sternum at the third intercostal space. Improvement followed the use of antistreptococcic serum, altogether 1030 c.c. being given.

Pye-Smith (*Lancet*, 1890, vol. ii. p. 821) at a meeting of the Hunterian

Society reported a case in which emboli had been observed in various arteries forming aneurysms. This case, regarded by him as ulcerative endocarditis, recovered.

Margaret Pease (*Lancet*, July 10, 1897, "Case of Recovery from Ulcerative Endocarditis"). Female, aged sixteen years. Palpitation, dyspnea, aching of joints, rashes, loud mitral systolic murmur, and faint aortic diastolic. Murmurs changed in character; a presystolic apical murmur appeared. Pericardial and pleural frictions. Spleen palpable. Temperature high and very irregular. At time of discharge (three months) was well except for aortic and mitral regurgitation. Antistreptococcus serum employed.

Albert Woldert (*Journal of the American Medical Association*, 1901, vol. xxxvi. p. 1343; Proceedings of the Philadelphia Pathological Society, "Case of Malignant Endocarditis (?); Recovery"). Female, aged nine years. Complained of pain in ankle and knee, which subsided in a few days. Loud, rough, systolic murmur was heard over heart. Afterward chilly sensations, with high and irregular fever, with sweating; anemia was profound. "In many respects it resembled a case of malignant endocarditis, but the child recovered, which argued against this view."

Dr. Sainsbury (*Lancet*, London, 1896, vol. ii., "A Case of Ulcerative Endocarditis Treated with Antistreptococcus Serum; Recovery"). Patient, male, aged thirteen years, admitted to hospital June 22, 1896, complaining of pain in the chest and heart, which first began June 6th. Sleeplessness; could not lie down; cough, weak, feverish, and later delirious at night. No history of rheumatism or chorea. As a baby had pertussis and measles. Temperature on admission 103.2°. Apex-beat in fifth interspace, four inches to the left of mid-sternal line. Dulness from first left intercostal space to right border of sternum. Thrill and double murmur at apex. Some impairment of breath sounds over both bases behind, and crepitation over whole right side of back. Liver and spleen not palpable. Urine negative. June 24th, violent delirium at night. Temperature 100°–101°. No bacteria found in blood June 25th. Marked dulness over left lung behind, and increase of vocal fremitus. Sputum rusty; no rigor. June 26th symmetrical, erythematous rash appeared on buttocks, spreading to rest of body. This lasted five days. July 1st, streptococci found in the blood. July 20th, temperature 102°. Cardiac dulness increasing. July 28th, temperature 104°. Cough, vomiting, bloody sputum. No rigor. Spleen palpable. Abdominal tenderness. Emaciation. Use of antistreptococcic serum begun. August 31st, patient up and around, feeling much better. Cardiac dulness normal. September 1st another injection, followed by temperature 102° and local symptoms. September 14th patient left hospital.

L. La Vastine (*Presse Méd.*, October 4, 1899, "Case of Infective Endocarditis which Occurred during Course of Puerperal Fever; Recovery"). Bacteriologic examination of blood showed presence of numerous streptococci and few staphylococci. The use of antistreptococcic serum was followed by improvement. Repeated doses by recovery.

Henry McClure (*Lancet*, 1887, vol. ii. p. 251, "Notes on Endocarditis; Reports of Two Cases, with Recovery"). Female, aged twenty-six years, complained first of pain referred to back of chest and shoulders. Temperature rose to 103°, and distinct murmur appeared over aortic cartilage. Patient became delirious, had involuntary evacuations, became slightly jaundiced, had a rapid pulse, an irregular temperature, at times as high as 105°, and in about two weeks several rigors. The aortic murmur became loud and harsh, and was carried well up into the vessels of the neck. Lungs negative. Slight albuminuria. Temperature normal for twenty-four hours for the first time at end of sixty-second day. Recovery with normal heart sounds at end of six months.

McClure's second case was a man of twenty years, who, with dysenteric symptoms, developed muscular and joint pains, fever, and a well-marked mitral murmur. A phlegmasia alba dolens appeared in the left leg. After two months, recovery, with normal heart findings.

Sir R. Douglas Powell (*Lancet*, London, 1898, vol. i. p. 982, "Case of Infective Endocarditis Treated with Yeast; Recovery"). Patient, male, aged twenty-one years. Had slight defect at aortic valve. Given to violent exercise. On May 15th he dined with a friend and was taken ill, with vomiting, faintness, fever 102°, and general malaise. Cardiac murmur, aortic regurgitant in character. Temperature continued to rise for four days. No rheumatic symptoms. On eighth day had chill. Temperature, which had been ranging from 100° to 102°, mounted to 105°. In four days had another chill; temperature, 105°. Sometimes he had two chills in one day. With chills sometimes had sharp pains in region of spleen; the latter was palpable. Aortic murmur marked, and a rough, mainly systolic murmur over left auricle. Yeast injected from July 1st to September 1st. Cardiac dulness increased upward and to right. Acute right pleurisy with effusion developed. Rigors now prolonged to intervals of six or seven days. Patient discharged September 1st and was seen in October; has been well since.

J. Mitchell Clarke (*Lancet*, London, 1900, vol. ii. p. 168, "A Case of Ulcerative Endocarditis, with Recovery under the Use of Antistreptococcic Serum"). Female, aged twenty-two years. Four years before, muscular rheumatism and pleurisy, with effusion. Admitted for dyspnea, precordial pains, slight swelling of ankles. Had enlarged heart and systolic murmur at apex. Temperature for three weeks from 100° to 101°. Then rigor, bronchopneumonia, higher temperature for four days. Temperature normal for a week, and then rose in irregular fashion, being, as a rule, normal or subnormal in the morning and from 100° to 104° in the evening. A new systolic murmur appeared in the pulmonary area, and a diastolic murmur in the aortic region. The pulse became weak and collapsing. The murmurs varied in intensity from day to day; the heart increased in size. The fever lasted for six weeks. The patient was very weak and anemic, but recovered, being treated with antistreptococcic serum, though no organisms were found in the blood. At the time of discharge no systolic murmur could be heard.

W. Hale White (*Lancet*, London, 1896, vol. i. p. 533, "Clinical Lecture on Gonorrheal Malignant Endocarditis"). During his lecture he refers to two

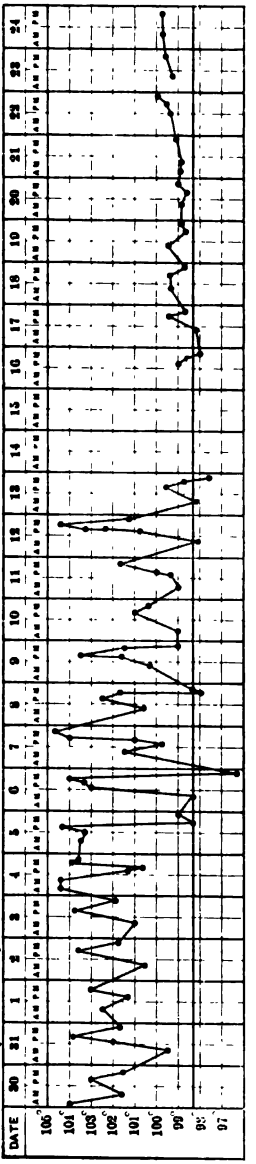
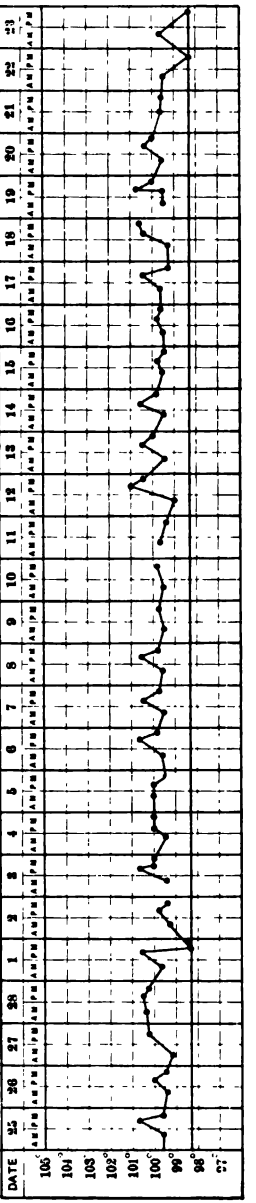


FIG. 1.



Temperature chart of my case of acute endocarditis.

cases with all the symptoms of malignant endocarditis. One, a woman, after her confinement, developed symptoms of endocarditis, and after three months' duration was apparently cured, the heart murmur having entirely disappeared. He also refers to another case which presented "every sign of the disease," and yet afterward was in excellent health and remained so for many months.

Charles G. Stockton (*Journal of the American Medical Association*, 1893, vol. xxi. p. 337, "Remarks on Ulcerative Endocarditis"). In his remarks on ulcerative endocarditis he recalls a case following vulvar abscess and accompanied by septic inflammation of the neck and right hand that went on to recovery.

Whitehead and Syers (*British Medical Journal*, November 2, 1901, "A Case of Ulcerative Endocarditis, with Recovery"). Male, aged thirty-five years. After earache a chill, some fever, and a distinct systolic murmur in the aortic area. Recurring rigors. Parotid gland became swollen. Temperature subnormal in morning, 105° in evening. Murmur increased in intensity. Patient very weak, and was in a desperate condition. Precordial friction. Dulness over base of left lung. Temperature normal after ten weeks. Loud systolic aortic murmur persisted at time of discharge of patient.

I have seen a child three years of age with a pneumococcic septicemia starting with throat symptoms—a nearly pure culture being obtained from this locality—causing otitis media and bronchopneumonia. At the end of ten days of serious illness a murmur could be heard at the apex, with systole; it varied in quality from day to day. With the appearance of the murmur there was an irregular temperature, a few chills, with the temperature jumping from subnormal to 105°, two crops of petechiæ, a splenic infarction, and a long-drawn-out convalescence, with persistent slight temperature for weeks, but with ultimate recovery of perfect health, yet with the signs persisting, even two years later, of a mitral regurgitation, muscular compensation being perfect. A five-year-old brother of this boy had at nearly the same time a similar sore-throat, with abundant pneumococci, an otitis media, and a pleurisy. A sister one year old had a light bronchitis. (Fig. 1.)

But anatomic proof that ulcerative endocarditis may heal is not lacking. At times there are found by the side of the characteristic acute lesions the evidences of scarring, the destructive process being replaced by a reparative one. Von Dusch (*Lehrbuch der Herzkrankheiten*, 1868, p. 173) remarks "that under favorable circumstances even the ulcerative endocarditis is capable of at least partially healing is shown by the perforations that have become converted into scarred, callous passages and communications between separate parts of the heart." Perhaps no observations in this line are more suggestive and instructive than those of Harbitz, of Christiania (*Om Endokardit*, Kristiania, 1897). He divides the acute endocarditides into two

classes: the toxic, of which the rheumatic form is the type, and the infectious. The latter class is subdivided into the two subclasses. In the one the endocarditis is clearly secondary to some recognizable suppurative process in some other part of the body.* It is not only infectious, but is infecting, its emboli commonly producing suppuration. The symptoms are fulminant, malignant, pyemic; death almost invariably results, and little or no evidence of an attempt at repair is found postmortem. The staphylococcus is the organism commonly present.

The other subclass of the infectious form is generally caused by the streptococcus or the pneumococcus, although the primary infection atrium may escape detection. Irregular or slight fever, chills, rheumatoid pains, anemia, hemorrhagic nephritis, non-suppurating embolic phenomena are present. The symptoms may last for weeks or months. The valves and mural endocardium show smaller or larger, irregular, warty or polypoid excrescences that are often rather firm, adherent at the base, at times showing calcification. There is often a large amount of fibrillary connective tissue, with few nuclei. At times also aneurysmal dilatation of the valves is seen. "On the whole these endocarditides give the impression that the process is old and in the stage of organization; it is tending toward healing." The more extensive destructive changes, ulceration, abscess, necrotic foci in the neighboring valve tissues, are generally slight or lacking. Bacteria (streptococci or pneumococci) are found in cover-slips, sections, cultures, and by inoculation. The condition is clearly an infectious one. Closely related to this form is one in which with similar anatomic findings the micro-organisms can be detected in sections, though in their reactions to stains, in their growth on culture media and in the bodies of inoculated animals they give proof of a low degree of vitality and virulency, or of absolute death. In other words, the process has healed and the patient's death has been due to mechanical and not septic causes. Harbitz has seen ten such cases. (*Deutsch. med. Woch.*, February 23, 1899, p. 123.)

Dr. L. Hektoen has kindly furnished me with specimens, drawings, and descriptions of the hearts from three cases where healing has partially taken place, and yet where the appearances are such as to warrant one in saying the process was distinctly infectious, if not ulcerative.

Autopsy Record, No. 987 (postmortem by Dr. H. G. Wells). *Anatomic Diagnosis.* Fibrous pericarditis; acute and chronic aortic and mitral endocarditis; healing perforation of aortic valve; vegetative aortitis; hypertrophy and dilatation of the heart; right hydrothorax and hydroperitoneum; chronic passive congestion of the lungs, liver, and spleen; old and recent infarcts of spleen and kidney; chronic nephritis; healed tuberculosis of lungs, pleura, and mediastinal glands; double inguinal hernia; right hydrocele; atrophy of testes; anomalous location of gall-bladder; tænia saginata.

Abstract from Record. There is complete fibrous obliteration of the pericardial cavity. The aortic valves are incompetent to the water test. The valve cusps are thick and sclerotic, with grayish vegetations upon the ventricular aspect. The posterior cusp has an interesting fenestration running a little below the free margin from the corpus Arantii to the lateral attachment of the valve. The margins of this fenestration are rounded and for

FIG. 2.

Case 987.

the most part smooth except near the corpus, where are typical vegetations. The upper margin is cord-like and about 2 to 4 mm. in diameter. The opening is about 1 cm. in length. There are similar vegetations upon the upper surface of the anterior mitral valve, the posterior being sclerotic. The heart weighs 600 grams. There are a few vegetations upon the aortic intima just above the aortic valves.

The endocardial vegetations when examined microscopically consist mostly of fibrin, with accumulations of mononuclear cells and large masses resembling coccal accumulations. No bacteriologic examination.

Abstract of History. H. H., male, aged twenty-four years, laborer, entered the hospital with a history of chills and fever some months ago, and cough and shortness of breath for about six weeks. The heart was enlarged, with systolic murmur at apex and rough diastolic murmur over the mid-sternum. The liver and spleen both enlarged. Capillary pulsation; water-

hammer pulse; prominent superficial veins. Temperature ranged from 98.6° to 102°. Sputum and urine normal.

Case No. 903 (postmortem by Dr. T. R. Crowder). *Anatomic Diagnosis.* Healed ulcerative (perforating) endocarditis; hypertrophy and dilatation of the heart; passive congestion of the lungs, liver, spleen, and kidneys; left hydrothorax, hydropericardium, ascites, anasarca, arteriosclerosis, miliary gummas of spleen and liver.

Abstract from Record. The pericardium is smooth. The aortic valves are incompetent to the water test. They are thick, fibrous, somewhat retracted, with rounded margins. The ventricular surfaces are somewhat roughened and finely granular, especially the anterior leaflet, which contains a rounded opening, 7 mm. in horizontal and 5 mm. in transverse diameter, situated

FIG. 3.

Case 903.

below the line of closure and extending to the base and right margin. The edges of this opening are smooth and rounded. The myocardium is firm, brown, with here and there whitish scars, especially in the papillary muscles The heart weighs 450 grams. There are large, somewhat gelatinous, raised areas in the beginning of the aorta, especially about the points of joint attachment of the aortic valves. The kidneys weigh 350 grams together, the surface is smooth, cortex reddish-gray, thicker than normal. Staphylococcus pyogenes aureus was isolated from the spleen and the lung, staphylococcus albus from the heart's blood, and bacillus coli from the liver.

History. W. M. M., colored, aged thirty years, gave a history of having been sick for two months, beginning with a cold, followed by swelling of the abdomen and of the ankles. He soon became short of breath, and eventually had to sit up at nights. He never expectorated blood. While there was

palpitation of the heart, he had never had pain. Had syphilis six years ago, smallpox five years ago.

Examination showed enlargement of the heart, roughening of the first sound at the apex, and a loud diastolic murmur to the left of the sternum, Corrigan pulse; scrotum, penis, and lower extremities edematous; fluid in the abdomen and chest. Temperature normal; pulse, 100 to 140. The urine contained a trace of albumin, hyaline, granular and epithelial casts; 400 c.c. per diem.

Case No. 1089 (postmortem by Dr. Wells). *Anatomic Diagnosis.* Healed ulcerative (perforating) endocarditis of the aortic valves; hypertrophy and dilatation of the heart; sclerosis of aorta and coronary arteries; anasarca, hydroperitoneum, hydrothorax, hydropericardium; compression collapse of both lungs; bronchitis; passive congestion and cirrhosis of liver and spleen; healed splenic infarcts; chronic nephritis and healed renal infarct.

Abstract from Record. The pericardium is smooth. The aortic valves are incompetent to the water test, pulmonary competent. The endocardium of the right heart is smooth. The mitral valves are somewhat thick and fibrous. The aortic valves are greatly deformed by irregular wart-like masses of fibrous tissue and of rather soft but not crumbling white tissue, in which are fine calcareous granules. The left posterior cusp shows a large circular perforation about 1 cm. in diameter; the superior margin consists of an irregularly nodular band 4 x 8 mm., while the inferior is thin and perfectly smooth. The aorta just above this perforation shows a few small, warty, rather firm outgrowths from the intima. The heart, especially the left ventricle, is much hypertrophied and dilated, and weighs 650 grams. The myocardium is firm, somewhat mottled, fibrous in the apices of the papillary muscles. There is considerable dilatation of the beginning of the aorta, with calcified spots in the thoracic part. The spleen is large (22 x 12 x 5 cm.), purplish in color, rather firm; the surface shows depressed, puckered, yellowish-white scars, the largest 3½ x 12 cm.; Malpighian bodies indistinct. The liver weighs 2250 grams, is rather firm, mottled, rather rough on the cut surfaces. After rapidly washing the surface of the outgrowths upon the aortic valves with from 1 to 1000 solution of bichloride of mercury and then rinsing thoroughly and repeatedly in sterile water, pieces were ground up in sterile water (1 to 2 cm.), from which several bouillon tubes were inoculated with three to four drops each. Several glycerin-agar and blood-serum smears were also made. All tubes remained sterile, and microbes were not found in the cover-slips. Cultures from the heart's blood, the liver and spleen sterile. Streptococcus pyogenes was isolated from the lungs.

History. P. N., male, aged fifty-one years, admitted September 17; died December 11, 1901. He gave a history of cough for two months, with some expectoration, but not of blood. For two weeks there had been dyspnea, mostly at night, with coincident swelling of the feet. Frequent urination since one year. Never sick before.

Examination showed a double murmur at the base and a systolic murmur

at the apex; diastolic pulsation of the veins in the neck; enlargement of the area of cardiac dulness. The liver extended three fingers' breadth below the costal arch; distinctly enlarged spleen; fluid in the abdomen and edema of the extremities. No fever; pulse, 70 to 90. The urine contained a trace of albumin, few granular and hyaline casts; 1800 c.c. in twenty-four hours. Blood showed 2,710,000 reds, 3200 whites, and 40 per cent. hemoglobin. On the 5th of October he spat up a good deal of blood.

FIG. 4.

Case 1089.

If recovery is possible it should make one more guarded as to prognosis, and particularly in those cases where the infectious agent is the pneumococcus or the streptococcus. It will be noted that in many of the cases reported as cures, where bacteria have been found in the blood, they have been streptococci or the treatment has been by streptococcus serum. It should be the aim of the physician to strive to determine the particular microbe that is at work in a given case, because of the value of such knowledge in making up a prognosis and to some extent because of its assistance in treatment. It is possible that some day we may be able to differentiate between the clinical picture presented by an endocarditis due to the streptococcus and the staphylococcus. Some serum test or some hemolytic reaction may be found of practical application. At least the blood can be examined bacteriologically, and this will often yield positive results. If one believes in the possibility of recovery, one will be more persistent in treatment. Rest, proper hygiene, nourishing food, iron and arsenic as blood-makers will be more urgently insisted upon; and some of the supposedly specific remedies, such as the serums or the Créde soluble salts of silver, can be employed, as has already been done by several observers, with what they believe to be beneficial effect.

DISCUSSION.

DR. THAYER: It occurred to me that it might be interesting in connection with this paper to show the chart of a case the symptoms of which justified the diagnosis of endocarditis of a malignant type, from which the patient is now apparently convalescent. The patient is a woman of about thirty years of age, who has been under my observation off and on for the past seven or eight years. She has had a well-marked mitral stenosis and insufficiency, and on several occasions has shown irregularly intermittent fever, lasting for periods of from a week or so to a month or two, which could be accounted for only on the assumption of the existence of an acute endocarditis. She is a trained nurse at present under the care of Dr. T. R. Brown, who has very kindly lent me the chart. The present attack began in the latter part of February with fever, associated with chills, delirium, an extremely irregular action of the heart, great prostration, and evidences of aortic insufficiency, which had not existed before. As may be seen by the chart, the temperature has been extremely irregular and at times very high, reaching even 106°, and there have been severe chills. But after a month's duration the temperature became normal or subnormal, and the patient is now apparently convalescent, with a distinct aortic lesion in addition to her previous trouble.

DR. KINNICUTT: I am very glad to be able to report a case like the one the author describes. It was a case of severe gonorrhea, and the patient was seen by me in consultation several weeks after the beginning of the affection. He had been under the care of a very careful gentleman, and previous to the infection had had no heart symptoms of any kind. He developed an endocarditis, affecting first the mitral valves, and when I saw him was extremely ill. The prognosis I gave was absolutely unfavorable, but, though that was two years ago, he made an entire recovery so far as the constitutional symptoms are concerned, and has ever since been an apparently well man.

DR. JANEWAY: A man came to my office every day in succession for a week with chills and a fever which reached daily 105°. Blood examinations were made frequently and no malarial organisms found. There was no heart murmur at first, but it developed later, and after several months' stay in the hospital, with evidences of infection of the lung and kidneys, he recovered. His pulmonic insufficiency remains.

There are cases, however, where we make a mistake. I made a diagnosis by telephone once on a patient in Hartford. They described the case to me as one of continued fever with loud murmurs and loss of pulsation in one arm. I thought it indicated an endocarditis of infectious type, and later I went there to see him, but convalescence had then been established. On the morning of my arrival the boy had been given up as a hopeless case, and when every one was watching him he suddenly awoke and said, "Damn it!

what are you all doing here?" When I arrived and examined him there was no murmur remaining at all, and the transformation had taken place within the day. This boy had had an obstructed artery by embolism as well as the other symptoms, and yet he recovered. It seemed to me probable that a simple thrombus had formed in his heart, and was the source of the embolism of the artery of the arm rather than an infectious endocarditis, with separation of a portion of the vegetations on a valve, as I had feared from the telephonic report of the case and his condition.

DR. SHATTUCK: I think I have seen two cases of ulcerative endocarditis recover—one under the use of antistreptococcus serum.

DR. JACOBI: I believe every one here has probably seen one or more cases of this kind, but I want to say that it is easier to make the mistake in adults than in children. A large number of these cases occur in children or young people, and the great vigor of the heart of the child makes it improbable that there is a functional murmur; when it occurs in the child it is organic; in the adult the heart has probably been diseased before, and the signs are not of the same import as in the child.

DR. OSLER: This case belongs to a special group, which I termed some years ago the cardiac. Recovery is excessively rare in septic cases, but when the endocarditis is of the recurring form associated with an old valvular lesion, the symptoms may subside. We have had at least three cases of that within the past few years.

MITOSIS IN CIRCULATING BLOOD.

By GEORGE DOCK, M.D.,
OF ANN ARBOR.

Mitotic figures were discovered in human blood corpuscles very soon after the characteristics of indirect cell division became known. Flemming,[13] in 1882, found cells showing typical figures in the blood of a leukemic patient under the care of Professor Quincke. Flemming rejected the view, obviously tempting at first glance, that the great increase of leukocytes in leukemia might be explained by indirect division, because the phenomenon was so rare that only one mitotic figure could be found among many thousand leukocytes. Moreover, he was uncertain whether the cells were really leukocytes in the usual sense, or the early stages of red blood corpuscles from the spleen or bone-marrow. Flemming's article is illustrated by pictures of mitoses in various stages, unstained, after treating the cells with acetic acid. In the following year Loewit[24] observed a mitotic figure in the blood of a patient with "severe secondary anemia." He was led by this to examine the blood of seven other cases of severe secondary anemia and two of leukemia. He found nucleated red corpuscles in only three cases, and in two of these indirect nuclear division. In 1884 Arnold[2] described, rather inadequately, karyokinetic processes in leukocytes. In 1886 Prus[33] noted the presence of distinct mitotic figures in the leukocytes from a case of "splenic leukemia." Hayem,[18] in 1889, described karyokinetic figures in the red corpuscles in the blood of an infant of ten months, with the diagnosis of leukemia. The clinical details are incomplete. The liver and spleen were enlarged. The red blood corpuscles numbered 2,712,500; leukocytes, 33,000. A statement that caused some comment at the time, but did not bring out any new work, was made by Spronck[37] in 1889. He hardened blood from the finger in Flemming's solution, embedded in celloidin, and stained sections of the mass with safranin. He claimed that the circulating leukocytes of healthy adults constantly contain mitoses in

the proportion of about one to one thousand. In leukemia he found an increase—six to one thousand. From this observation it might be supposed that mitotic figures should be encountered frequently in estimations of leukocytes, and since this is obviously not so, Spronck has been generally discredited. It is true that he may have mistaken polymorphous nuclei for mitotic figures; but, on the other hand, some observations I have made in leukemic blood treated in the same way have led me to think that mitoses are more likely to be found in sections of hardened blood than in smears. But control observations would be tedious and not very profitable. Obrastzow[31] found a diaster in the blood of a case of acute leukemia. H. F. Mueller[28] examined two cases of leukemia, in which he found karyokinetic figures in all stages, though rarely. He later[29] described a case with large numbers of mitotic nuclei, so many that one figure could be found while counting "several hundred" leukocytes. The process occurred in both red and white corpuscles. The later article is illustrated by excellent pictures of karyokinetic leukocytes, one of the dividing nuclei being atypical (tripolar). Von Noorden[30] saw a mitotic red cell in a case of pernicious anemia, and Dorn,[10] quoted by Juenger, found many such cells in the same disease. In the same year, 1891, Luzet,[25 26] by asserting that "infantile splenic pseudoleukemia" is "characterized especially by the presence of large numbers of nucleated red blood corpuscles, many of which show signs of karyokinesis," called forth a great deal of work on the microscopic features of blood in the condition named and in the peculiarities of infantile blood in general. Baginsky[5] found suggestions of karyokinesis in the nucleated red cells in cases of infantile anemia with enlarged spleen, but was not prepared to accept the newly described condition as a distinct disease. He could not exclude an intimate relationship between it and rickets. Fischl,[12] in fact, soon found mitotic figures in the red cells in cases of anemia in rickets, while Hock and Schlesinger,[20] who denied the existence of characteristic blood changes in infantile splenic pseudoleukemia, observed mitotic figures in the red (?) corpuscles of both sick and healthy nurslings. Alt and Weiss,[1] however, agreed with Luzet regarding the blood picture of anemia splenica pseudoleukemia, having found mitotic red cells in that disease, but not in the blood of several other anemic infants. Wertheim,[42] in studying leukemic blood with reference to the origin of the

red and white cells, found karyokinetic figures in the (finger) blood of thirteen cases of mixed leukemia. The figures had the same characteristics as those in embryonic blood. In a case of lymphatic leukemia he failed to find mitoses. He explained the failure of others to observe the process in leukemia by neglect of stained preparations or by a too exclusive use of granule stains. He found that the number of figures varied in different cases and in the same case at different times. In some a whole preparation had to be searched to find a few cells showing the process. Like many other observers of the same period, Wertheim supposed that both red and white corpuscles took their origin from a common hemoglobin-free ancestor, and he saw nothing in his investigations to change his opinion. Rieder[34] found an "astonishing number of mitoses" in the blood from a case of myelogenous leukemia, both in "normal leukocytes" and "myelocytes." Troje[41] studied the mitotic figures in red and white corpuscles from a case of acute leukemia, and clearly recognized and stated the differences of both kinds of cells in all stages of development. About the same time Bastianelli[6] described and figured mitotic leukocytes in the blood of malarial patients, but the observation arrested little attention, probably on account of the greater importance of the author's researches on malaria published at the same time. Monti and Berggruen[27] noted karyokinetic figures in blood in the course of their careful study of the blood in infancy. Finding these in only two out of four cases of infantile splenic pseudoleukemia, they doubted the importance of the sign in the diagnosis of von Jaksch's disease. They also found a mitotic red cell in a case of "chronic anemia gravis cum leukocytosis," and indications of indirect nuclear division in one case of leukemia. Askanazy[3] reported a case of rapidly fatal pernicious anemia, with large numbers of megaloblasts, a few normoblasts, and some cells difficult to classify. Many cells showed mitotic figures in all stages of division. Two or three could be found in every cover-glass preparation. Askanazy's illustrations include one of a tripolar mitosis. In a later article[4] the same observer stated that he had frequently found indirect nuclear division in megaloglasts in severe anemias, as in a case of bothriocephalus anemia, the subject of the later contribution. Schauman[36] also found mitoses in red corpuscles in two out of twenty-six cases of bothriocephalus anemia. In 1895 Glockner[16] noticed mitotic red cells in two out of

four cases of splenic anemia in infants. Stengel[38] figured mitoses in blood corpuscles in his comprehensive article in 1896. Those in red corpuscles he thought were comparatively rare, but those in leukocytes more frequent, especially in the large mononuclear cells. Writing in the same year, Grawitz[17] seemed to have had no experience with karyokinesis in blood cells, mentioning only cells with "two nuclei lying opposite each other." Pick[32] demonstrated at the Congress for Internal Medicine, in 1897, preparations containing beautiful mitotic figures in red corpuscles from a case of leukemia. The illustration in the second edition of von Limbeck's book was taken from these preparations. Von Limbeck[23] does not mention any observations of his own. Both Cabot[7] and Coles[8] figured and mentioned mitoses in their text-books, and Lazarus[22] thought that mitotic figures "have probably been seen by all who have had opportunities for examining the blood in pernicious anemia, especially in severe cases." Taylor,[40] in his extensive and painstaking observations in leukemia, found two typical karyokinetic cells, probably gigantoblasts, in two cases, and one leukocyte with indirect division. Juenger[21] was the first to make a more particular study of the subject of nucleated red blood corpuscles. His material was derived from cases of leukemia, and he made many important observations on mitosis. He questioned the belief of Mueller that karyokinetic red cells in leukemia are merely swept out of the places where they are formed, assuming rather that such phenomena indicate metaplastic processes in bone-marrow. He agreed with Troje that no transition forms could be found from mitotic leukocytes to red corpuscles. According to him, both nucleus and protoplasm have unmistakable features in each variety of blood-cell. Juenger's article is well illustrated. Frese,[14] in his article on metastatic cancer of bones, mentions a case of cancer of the stomach with numerous metastases, and with severe anemia (hemoglobin, 21; red corpuscles, 900,000; leukocytes, 9220), with a few mitotic megaloblasts. He refers to a case of cancer of the prostate with metastases, reported by Braun (*Wiener med. Wochenschrift*, 1896, No. 12), with mitoses. Sabrazès[35] claimed to have found karyokinesis in the leukemia of infants. Mitosis in leukocytes (myelocytes) he thought rare in leukemia; in red cells, not so rare. Hayem[19] made the interesting statement in 1900 that he had never seen mitotic leukocytes in leukemia. "The red cells, on the contrary," he said, "present these, not

only in the disease called, without good reason, infantile pseudoleukemia, but also in leukemia of adults." Geissler and Japha,[15] whose work on the blood of children contains many observations of value, give two cases of rickets with enlarged spleen and moderate anemia in which mitoses occurred in red cells. Strauss and Rohnstein[30] found a mitotic megaloblast in one of three cases of bothriocephalus anemia observed by them. Ewing[11] quite recently has mentioned mitosis in red corpuscles, megaloblasts especially, in pernicious anemia. He found them usually only in the severer stages of the disease. A typical mitosis he considered "one of the most significant pathological signs within the range of blood analysis."

On the whole, the number of reports on mitosis in circulating blood is small, especially in comparison with the extensive literature on blood. I have tried in the résumé above to include all the important references, but have omitted several allusions, some of which are almost as definite as one or two I have quoted, because they add nothing to the development of the subject.

The divergent results and views of previous writers seemed to me to render worth while a report of my own observations. These were not made primarily for the purpose of finding mitoses. They were made in the course of routine examinations in ordinary clinical work, and extend over a number of years and a somewhat extensive material. My interest was excited especially by the statement of Spronck, referred to above, because my observations up to that time had revealed very few mitoses. The material from patients under my care includes twenty-two cases of mixed-celled (so-called myelogenous) leukemia, three cases of chronic small-celled leukemia, two cases of acute leukemia, two of fatal megaloblastic anemia, apparently acute, one of which has been reported,[9] forty cases of chronic pernicious anemia, and several hundred cases of secondary anemias, chlorosis, and leukocytosis. Mitotic figures were found in both cases of acute anemia; in two cases of chronic pernicious anemia; one case of severe anemia with splenomegaly, of doubtful origin, in an infant, not rhachitic, but possibly syphilitic; in eight cases of myelogenous leukemia, and one case of acute leukemia. Many of the patients with pernicious anemia were seen only during short periods.

Most of my examinations were made on preparations fixed in ether and alcohol and stained with hematoxylin and eosin. This gives

fairly good results, though better ones can be obtained by following Mueller's plan of treating the preparations with picric acid and staining slowly in weak hematoxylin solution. With the former method errors in confusing mitotic cells with polymorphonuclear leukocytes are easily avoided by washing out the eosin until the leukocyte bodies are colorless. With Ehrlich's triacid stain mitotic cells can be recognized, but often with difficulty.

As some of the illustrations show, the ordinary methods of preparing blood for clinical purposes preserve the mitotic figures very well. The skeins, however, must be more or less compressed by the flattening of the cells in drying. In one case of leukemia beautiful preparations were made for me by Dr. (then Mr.) Carlin Philips, according to Spronck's method. The sections stained with safranin seemed to show more mitoses, and certainly more typical ones, than did the cover-glass preparations.

As regards the kinds of cells containing mitoses, these were the red cells in seven cases of leukemia and in the severe anemias. In three cases of leukemia only the red cells showed mitoses. In one case of leukemia only the myelocytes were involved; in fact, all the mitotic leukocytes seemed to be myelocytes (of Ehrlich). I have never encountered a lymphocyte undergoing mitosis in the blood, though in two of my cases of small-celled leukemia I carefully examined scores of preparations. Nor have I seen mitosis in what seemed to be a polymorphonuclear leukocyte. In the case of acute leukemia, with about 540 nucleated red cells per cubic millimeter, one red cell, apparently a megaloblast, contained a good diaster. In the anemias all the mitoses were in red cells, usually megaloblasts. The occurrence of mitotic figures in normoblasts has rarely been noticed by previous writers, but in leukemia many of the most unmistakable figures, in my experience, have been in cells not much above the average size. Some years ago I expressed the opinion that mitoses are more frequently found in white than in red cells in leukemia. A larger experience has made me reverse this.

The number of mitotic figures varies very much, not only in different cases, but in the same case at different times. In some cases only a single mitosis can be found in a thorough search of several preparations. In a case of leukemia, on the other hand, I found in one cover-glass preparation six diasters in early stages, five more with

constriction of the cell-body, and twenty-three equatorial plates in red cells, and eight diasters and two equatorial plates in leukocytes. This includes only well-preserved figures. Many imperfect figures were present in the same preparation, but as these cannot all be sharply distinguished from fragmented nuclei it seems better to reject them all. Much depends upon good spreads. Askanazy has told us that he found several mitoses in one preparation and none in another made at the same time, and I have had a similar experience. It seems better to have the film rather thick, though with the corpuscles as nearly as possible all flat. That Wertheim found mitoses in all of the thirteen cases of leukemia seems rather hard to believe, yet it may be possible as the result of an unusual series of cases. I have had four consecutive cases with mitoses in leukemia.

Regarding the phases of mitoses encountered in blood, there are some interesting facts. The preparatory phase, in which the chromatin shows a coarse meshwork, is strongly suggested by many nucleated red cells, especially certain megaloblasts, and many normoblasts in leukemic blood. The earliest appearance that can be positively identified—the spirem with rather coarse skein—has been rare in my preparations. It is shown in Figs. 1 and 4.

The metaphase is rather more frequent (2, 3, 9, 10). The commonest figure by far in red cells and leukocytes is the diaster, without signs of division of the cell body (Figs. 5, 6, 11, 12, 13, 15, 16), and somewhat less frequently a still later stage, with more or less constriction or division (7, 8). Achromatic spindles I have never encountered in films, but have in sections. Centrosomes are not easy to identify. Sometimes there are small particles of chromatin that seem to represent them. Fragmentation and other evidences of degeneration of the nucleus are not rare in mitotic blood cells. Hyperchromatic nuclei occur sometimes, Plate I., Fig. 4, being a marked example. There are differences in the nuclear figures of the red and white cells, and I have seen nothing to indicate the transition from one to the other. The mitoses in red cells are usually plumper in the later stages, and stain more deeply in all stages than do those in myelocytes. This is true also of cells in blood hardened en masse. The red cells vary in intensity of color, though the differences in many instances are doubtless due to accidental variations in spreading.

The mitotic red cells are usually orthochromatic, but many show polychromatophilia in various degrees. (See Plate II., Fig. 3.) Punctate mitotic cells, such as Lazarus pictures, I have found in only a few instances in pernicious anemia. A more common appearance is polychromatophilia, with a loss of the usual luster of the protoplasm in part, usually the outer part, of the affected cell. (See Plate II., Fig. 2.) This latter change can hardly be anything but a degenerative one, whereas the polychromatophilia represents conditions that are normal in embryonic blood. Vacuoles and fissures may also be found in mitotic red cells. They are probably in part artefacts.

The mitotic leukocytes usually have a distinctly granular, spongy, or foamy protoplasm, and in the triacid stain show fine neutrophile granules. Sometimes the protoplasm looks more delicate, as if degenerated (see Plate II., Fig. 5), and in some cases it takes the nuclear stain more or less distinctly, while the nuclear figures are unusually pale.

In endeavoring to discover the significance of the presence of mitotic processes in circulating blood I have examined the associated conditions. The mitotic red cells in leukemia were not encountered only in those cases with the greatest anemia, nor were they always encountered in such cases. The red cells in the seven cases ranged from 2,230,000 to 3,587,000, and in several cases with less than two and a quarter million red cells per c.mm. there were no mitoses.

In all cases of leukemia with red cells in mitosis there were many nucleated reds—from 1100 to 20,800 per c.mm. in my seven cases—but there were other cases with many nucleated red cells—from 2000 to 14,000 per c.mm.—without mitoses in the red cells. There is no constant relation between these ; but in a single case there is sometimes a relation between the number of mitotic red cells and of all nucleated red corpuscles. Thus in one case with very many mitotic reds there were 7378 nucleated reds per c.mm., the total red count being 2,500,000. The number of nucleated reds fell to 2100 and then 416 per c.mm., with a decreasing number of mitoses, and finally, with 258 nucleated red cells in the cubic millimeter, no mitoses could be found. In the pernicious anemias, with sometimes large numbers of mitotic figures, there were only from 232 to 400 nucleated red cells per c.mm., except in the acute case already reported, in which there were up to 20,000 or more.

The mitotic myelocytes were usually found in cases with high leukocytosis—*i. e.*, 165,000, 3,000,000, 608,000, 700,000, and 882,000. The last-mentioned case had by far the most, perhaps more than all the others together, while the case with 165,000 leukocytes had very few and the one with 300,000 still less. But in another case, with 600,000 leukocytes, no mitotic myelocytes could be found. The cases with mitotic myelocytes in my series were those that had the largest proportion of myelocytes—viz., 158,000, 182,000, 183,000, 212,000, and 323,000 per c.mm. Only one case without mitotic myelocytes had a larger number than the lowest of them, and in that case the leukocytosis fell soon and the myelocytes became much less numerous.

These facts seem to me to go far toward an explanation of the phenomenon. Though our knowledge of the circulation in the blood-forming organs is too imperfect to permit clear conceptions, the presence of both nucleated red cells and myelocytes indicates a defect in the process. Chemotactic processes have been supposed to explain the entrance of the myelocytes into the circulation. The presence of mitoses in these cells would be easily explained by assuming that cell formation is active and that some of the cells happen to migrate in some stage of division. Even if the myelocytes are swept into the circulation in a passive way we should expect to find division processes in some of them.

In the case of the nucleated red cells one is tempted to see a teleologic process and to suppose that evidences of mitosis indicate active regeneration of the blood. This, however, is difficult to prove. In the case of leukemia with many mitoses, gradually decreasing, the red cells increased about one million per c.mm. But in other cases there was no perceptible gain. In chronic pernicious anemia the mitosis in both my cases appeared in periods of active improvement. The same thing was true of a patient whose blood I had the privilege of examining with my colleague, Dr. Arneill. But in other cases of pernicious anemia, at times of rapid improvement, I have failed to find mitotic cells, and in one of the two cases I had watched the patient through two previous stages of improvement, equally rapid, without finding any mitotic cells. In my two cases of acute fatal anemia mitoses were very numerous. Unfortunately, it is not possible in such cases to know how much blood-

destruction is going on. Improvements in our methods may be able to throw more light on this question. At present I think we are not justified in claiming that mitosis in circulating blood has a definite diagnostic or prognostic value. In general it coincides with the occurrence of many nucleated red cells or myelocytes in the circulation. The differentiation between mitotic red and white cells, as I have said above, is easy. The question whether the mitotic red cells are normoblasts or megaloblasts is, of course, important; but the mitosis itself does not change materially the prognostic status of these cells. A few mitotic megaloblasts do not indicate a bad prognosis in the immediate future. One of my patients lived for a year in comparative health after such mitoses were found, and another has made a remarkable improvement in the four months since the observation.

Atypical mitosis is apparently rather more serious in its indication than the normal process, but probably only because it is found with extremely active cell development, and because this is often a part of unfavorable conditions.

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PLATE I.

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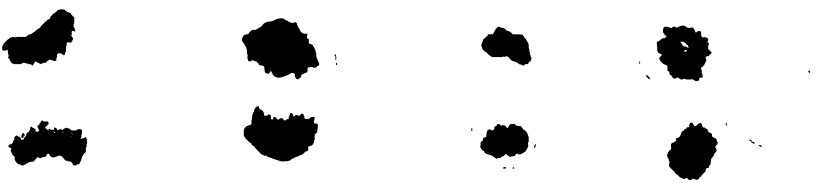

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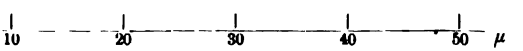
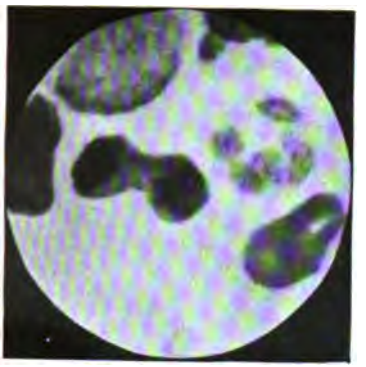


PLATE II.



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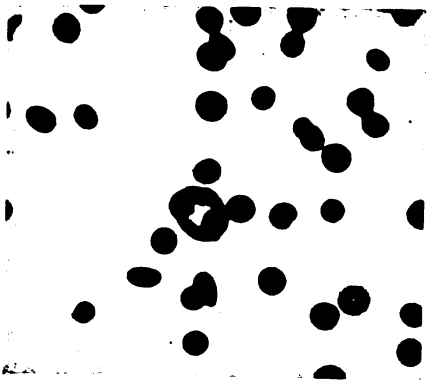

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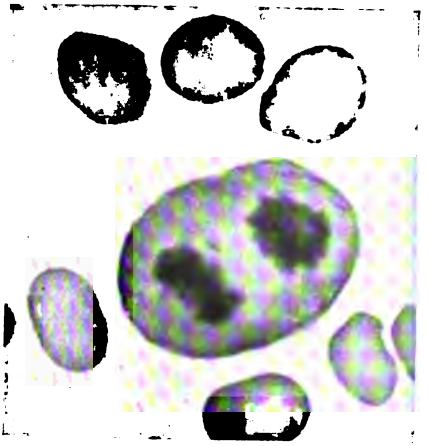

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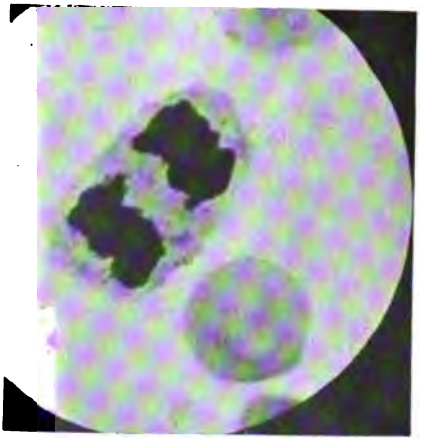

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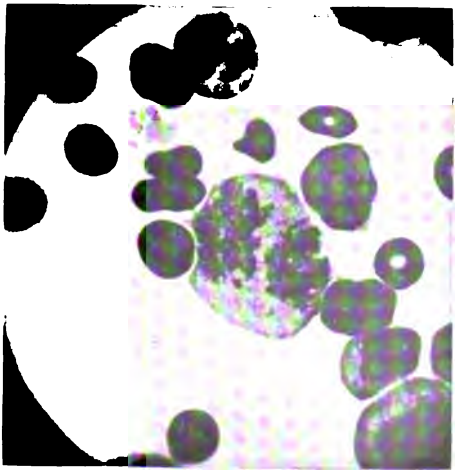

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EXPLANATION OF PLATES.

PLATE I.

Camera lucida drawings; Zeiss one-twelfth inch oil immersion, No. 4 eye-piece; tube 160 mm. (See scale.)

FIGS. 1-7.—Red corpuscles from a case of myelogenous leukemia.
FIG. 8.—Red cell from another case.
FIGS. 9-12.—Myelocytes from two cases of leukemia.
FIG. 13.—Red cell, infantile anemia.
FIGS. 14-16.—Megaloblasts from case of fatal anemia following endothelioma of the nose.

PLATE II.

(Photomicrographs by Dr. Charles S. Bond, Richmond, Ind.)

FIG. 1.—Normoblast from case of leukemia. × 1500.
FIG. 2.—Field with degenerated megaloblast from case of endothelioma of nose. × 500.
FIGS. 3 and 4.—Megaloblasts from the same case. × 2000.
FIG. 5.—Degenerated myelocyte; leukemia. × 1000.
FIG. 6.—Myelocyte; leukemia. × 1500.

THE PATHOLOGY OF PERNICIOUS ANEMIA, WITH SPECIAL REFERENCE TO CHANGES OCCURRING IN THE HEMOLYMPH NODES (EIGHT AUTOPSY CASES).

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The pathology of pernicious anemia as given in the most commonly used text-books of to-day contains but scant reference to the lymph glands, and no mention at all of the hemolymph nodes. Though much attention has been paid in recent years to the changes occurring in the spleen and bone-marrow, the lymphatic structures have been practically disregarded as a possible factor in the pathogenesis of the disease.

In Barclay's case of "Death from Anemia" (1851) no mention is made of changes in the lymph glands.

The classical description of Addison (1855) states that in "idiopathic anemia" there is "no renal, splenic, miasmatic, glandular, strumous, or malignant disease."

In one of Wilks' cases (1857) the lymph glands were described as "healthy." Lebert (1858) does not mention the lymph glands. Bristowe, in the same year, reported a case in which the bronchial, mesenteric, and other abdominal glands were described as healthy. No mention of lymph gland changes is made by Cazenave in 1860. In the same year Habershon states that there is no lymphatic disease in "idiopathic anemia." Grohe (1861) does not mention the lymphatic glands in the report of his case. Neither is there any mention of lymphatic gland changes in the cases observed by Wagner (1864), Trousseau (1868), and Perroud (1869).

Biermer's celebrated observations on "Progressive Pernicious Anemia" (1868–1872) contain no mention of the condition of the lymph glands. Likewise in the cases reported by King and Gusserow (1871) no mention is made of these structures. In an unpublished

case of Pye-Smith, observed in the same year, slight enlargement of the lumbar glands was noted. In Sörenson's case (1874) no swelling of the lymph glands was noticed. Immermann, in the same year, does not mention the condition of the lymph glands.

In 1875 Pepper stated positively that in pernicious anemia there is "no affection whatever of the lymphatic glands." Immermann, in Ziemssen's *Cyclopædia*, stated that "the spleen, the lymphatic glands, the marrow of the bones show no signs of hyperplastic activity or of anything abnormal beyond extreme paleness." In the same year Krieg mentions the mesenteric glands in one case as atrophic; and Schumann found in one case that the "mesenteric glands were enlarged, grayish-white, spotted with red, and hemorrhagic." Two cases reported by Pye-Smith showed no changes in the lymphatic nodes.

In 1876 cases were reported by Lebert, Burger, Scheby-Buch, and Bradbury without mention of the lymph glands. In the same year Ferrand reported a case with "swelling of the mesenteric glands;" and Habershon one in which "no glandular enlargement was found." Quincke (1877) observed one case with "slight swelling of the lymph glands." Cases were reported in this year by Mackern, Stricker, Rosenstein, and Andrew without mention of the lymph glands; Bramwell one case in which the mesenteric glands were somewhat enlarged; and Purser a case in which the bronchial glands are mentioned as normal and the mesenteric glands not enlarged. Lépine's review of the fifty cases published up to this year contains the statement that under "essential anemia" should be included also cases in which there was a decided affection of spleen, lymph glands, or marrow. No details of these changes are given.

In 1877 appeared also the first monograph on pernicious anemia—that of Müller. Sixty-two cases with thirty-nine autopsies were analyzed. In only one case was the condition of the lymph glands mentioned, Case XXXIV., in which the mesenteric glands were of a striking bright-red color.

In 1878 the more elaborate work of Eichhorst, *Die Progressive Perniciöze Anämie*, was published. This work was based upon the analysis of eighty-four cases collected from the literature, including those of Müller, and seven cases of his own, eighty-nine autopsies in all. The changes occurring in the lymph glands were summed up

by Eichhorst as follows, and, inasmuch as this summary forms the chief basis for the statements found in subsequent text-books, it is quoted in full:

"*Lymph Glands.* In the superficial lymph glands, which may be easily and thoroughly examined by the hand, no enlargement in pernicious anemia has been found. In my fourth observation the glands of the groin were hard and scarcely larger than peas, yet any one who has examined many patients knows that this condition is a very common, almost normal occurrence.

"Even so rarely have I found enlargement of the mediastinal and thoracic glands in my autopsy cases, or is such condition mentioned in the literature.

"From this the impression is gathered that the lymph glands in the above mentioned regions are able to offer a greater resistance to the irritation caused by the changed quality of the blood than is the case with the spleen, although they correspond so closely in structure with the latter.

"Quite different is the case with the mesenteric glands. Repeatedly have changes been found in them in pernicious anemia, and it is possible that the number of such observations would be greater if, as there is good reason to suspect, they had not frequently been left unexamined.

"Krieg found them atrophic in a man who had a dilatation of the stomach.

"Müller observed in one case that they appeared very prominent because of the contrast of their bright-red color against the surrounding anemic tissues.

"Ferrand and Quincke state that the glands were swollen. Schumann found likewise a swelling of the mesenteric lymph glands. On section they appeared of a grayish-white color, speckled and spotted with red. In the last three observations it is important to make prominent the fact that the swelling of the lymph glands existed independently of any splenic enlargement, the latter not being present in these cases. Moreover, disturbances of digestion were not present to any degree worthy of mention in the cases of Quincke and Schumann.

"Swelling of the mesenteric lymph gland was noted in three of my five cases which came to autopsy. They reached the size of a

hazelnut. The glands were of rather firm consistency, and on section appeared bright red. It seemed remarkable to me that the red color was not homogeneous, but spotted, without it being possible, either with the naked eye or with the help of the microscope, to discover true hemorrhages. No unusual cellular elements were found in the glands, and their enlargement depended upon a hyperplastic condition.

"With relation to the causes of this hyperplasia I might here assume the explanation which I have offered for the origin of the splenic hyperplasia. I take it that we have to do here with subsequent conditions and secondary changes dependent upon the abnormal constitution of the blood.

"In my fifth observation the simple hyperplasia was accompanied by another anatomic appearance; small caseous areas were found in the swollen glands. I have been able to collect from the literature many cases from which it appears that even hyperplastic lymph glands are inclined to other metamorphoses. Slawjansky many years ago described two cases of leukemia lienolymphatica in which the enlarged lymph glands showed in many places a pronounced caseous metaphorphosis. Schnitzer has reported from Frerich's clinic a case of pseudoleukemia in which the enlarged lymphatic glands in the neighborhood of the cardia appeared medullary infiltrated. Caton has under the same conditions observed amyloid change in the lymph gland tumors."

In 1878 three cases were reported by Mackenzie, who summarized the clinical and pathologic features of the disease, stating that "the lymphatic glands are usually not enlarged."

In 1880 Weigert reported a remarkable case which is noteworthy as being the first case of pernicious anemia in which changes of importance were noted in the lymph glands. As this case is constantly referred to in the subsequent literature, I quote in full those portions of his description relating to the lymphatic changes: "The axillary and inguinal glands are swollen to red masses, and are surrounded by a delicate network of dilated lymph vessels filled with red transparent fluid. . . . Cervical lymph glands swollen to red masses, surrounded especially from above by a very delicate network of greatly dilated lymph vessels filled with red transparent fluid. On the right side of the ascending aorta, in the upper half of the thoracic portion

of the same, lies a very rich, remarkable network of knotty lymph vessels filled with a clear red fluid, these communicating frequently with the thoracic duct. The network has a breadth of 2 cm. . . . Mesenteric, retroperitoneal, portal, and omental lymph glands and lymph vessels similar to the above. . . . The microscopic examination of the lymph glands showed a marked dilatation of the lymph sinus and the presence in the same of a lymph uncommonly rich in blood. A similar fluid was observed in the lymph vessels."

In explanation of this case Weigert ruled out the hemorrhages present as the causal factor, in that they were too small to account for the presence of so much blood in the lymphatics, and in many places no hemorrhages were present in the area supplying the lymphatics, though the latter were filled with blood. At first inclined to explain the process as due to an increased permeability of the vessel walls for red cells and blood plasma, but not to such a degree as to form visible hemorrhages, Weigert was led later to regard it as due most probably to a compensatory hematopoietic function of the lymph glands for the marrow. He was not able to make out the presence of nucleated red cells. The dilatation of the lymph vessels was, at any rate, not due to obstruction.

Hartshorne, in Reynolds' *System of Medicine* (1880), states that there is "no alteration of lymphatic glands" in pernicious anemia. Coupland, in the *Goulstonian Lectures on Anemia* (1881), says that there are no changes in the lymphatic glands in this disease.

In 1883 Pye-Smith gave a clinical and pathologic analysis of the disease, based upon a study of 103 autopsy cases collected from the literature (including Müller's and Eichhorst's) and one new case observed by himself, concluding from this analysis that "in genuine cases of idiopathic anemia the lymph glands are not enlarged, nor are the solitary or agminated lymph follicles. Slight swelling of the mesenteric lympharia has been occasionally noticed, due, perhaps, to precedent diarrhea."

Osler, in Pepper's *System of Medicine* (1885), says: "The lymph glands are, as a rule, normal in size and appearance. In three instances I have found them decidedly smaller than normal, and in two they had a rich red color, and on section looked more like spleen tissue than lymph gland. Weigert has noted the same appearance. In one of the cases there were nucleated red corpuscles in the glands,

as has been observed by Rindfleisch in a case of rickets, and more recently in tuberculosis."

In Fagge's *Practice* (1886) the lymph glands are not mentioned in the article on pernicious anemia. In the same year Flint says: "The lymph glands, which are usually normal in appearance, may be somewhat swollen and of a deep-red color, containing an unusual number of red blood corpuscles, among which may be nucleated red corpuscles." In 1887 Bartholow says that the "disease is distinguished from leukemia by the normal condition of spleen, liver, and lymphatics."

Eichhorst (1891): "Mesenteric glands often swollen, hyperemic in places, and speckled with blood. In one case all the glands were swollen and red, the lymphatics dilated and contained bloody lymph."

Osler (Pepper's *American Text-book*, 1894): "The lymph glands may be unchanged, though in three of my cases they were of a deep-red color resembling spleen tissue—a condition which has been noted by Weigert."

Grawitz (1896) refers to Weigert's and Neumann's cases. Tyson, in the same year, says there is "absence of lymphatic enlargement or involvement of the spleen except in small degree."

Anders' *Practice* (1897): "The lymph glands are often somewhat swollen and intensely red in color, owing to the unusual number of red corpuscles, some of which are nucleated."

Ehrlich and Lazarus (Nothnagel's *Specielle Pathologie u. Therapie*, 1898): "In a fairly large number of cases, which otherwise showed nothing characteristic, especially no splenic enlargement, the mesenteric lymph glands were found to be swollen (Eichhorst, Quincke, etc.). From the microscopic examination of the first named observer the enlargement appeared as a pure hyperplasia; only in one case were the swollen glands caseous in the centre. What relation these enlargements of the lymph glands bear to the disease process, or whether they stand related to local disturbances in the intestinal tract or to the disturbed abnormal function of the bone-marrow cannot be decided. The blood findings give no evidence of increased activity of the lymph glands in so far as the production of lymphocytes is concerned."

Eichhorst (Eulenberg's *Real-Encyclopœdia*, 1898): "Swelling of

the mesenteric glands repeatedly found. Other lymph glands also sometimes enlarged. Weigert described the presence of bloody lymph in the dilated lymph vessels."

In Bramwell's *Anemia and Diseases of the Blood-forming Organs* (1899) no mention is made of changes in the lymph glands. Laache (Ebstein and Schwalbe's *Handbook*, 1900) states that the mesenteric glands are often swollen, and refers to Weigert's case.

Howard (*Reference Hand-book of the Medical Sciences*, 1900): "The lymph glands are usually normal. In a few instances the lymphatic glands of the mesentery have been recorded as enlarged, this change being due, as Pye-Smith suggests, to a previous diarrhea. In one case the lumbar lymphatic glands were enlarged."

Strümpell: "The lymph glands do not usually present any changes in pernicious anemia. If they are much altered it is probable that the disease is quite a different one (pseudoleukemia).

Osler (1901): "The lymph glands may be of a deep-red color."

Cabot (*American Text-book of Pathology*, 1901): "The spleen and lymph glands show no changes in the majority of cases."

Hunter (*Pernicious Anemia*, 1901): "Few or no changes have been described in connection with the lymphatic glands. The absence of any enlargement or other marked change is a notable feature (Addison), distinguishing this form of anemia at once from leukocythemia and other forms of glandular anemia, and this observation has been confirmed by all subsequent observers.

"In some cases, however (Eichhorst's), the mesenteric glands have presented some appearance of redness and swelling. Another case is described by Weigert, in which, along with dilatation of the lymphatics of the neck and of the mesenteric, portal, omental, and retroperitoneal lymphatics, there was also some swelling of the mesenteric glands, their sinuses being filled with lymph containing many red corpuscles. This case Weigert was inclined to regard as one of supplementary blood formation on the part of the glands, but it stands alone, and no great value can, therefore, be attached to it. No abnormal microscopic appearances have been noted; and as regards the importance to be attached to the appearance of redness and swelling, it is only necessary to state that precisely similar changes were found by Neumann in the case of anemia resulting from severe metrorrhagia already referred to. In this case likewise, with the

exception of a very few nucleated red corpuscles, no changes were found microscopically."

In many of the text-books published within the last several years (Schmaus, Kaufmann, Ziegler, Musser, Stengel, Coplin, Coles, Thompson, Ewing, *Twentieth Century Practice*, etc.) no mention is made of changes in the lymph glands in this disease.

Reviewing critically those statements above in which changes are said to have occurred in the lymph glands, it will be seen that practically, with the exception of Osler's observations, our knowledge of lymph gland changes in pernicious anemia is based upon Eichhorst's summary and the case reported by Weigert. The statements regarding the frequent occurrence of swelling of the mesenteric glands, when sifted down in the autopsy reports in the literature, are in reality based upon few observations of this condition; and Eichhorst's statement that these changes have been repeatedly observed is not borne out by the autopsy notes of the cases upon which he bases his summary. I have analyzed with respect to this point 173 autopsies of pernicious anemia collected from the literature since the appearance of Eichhorst's monograph. In 142 of these cases no mention of the lymph glands is made. In 14 cases the statement is "no enlarged lymphatics" in 4; "mesenteric glands not enlarged" in 4; "lymph glands normal" in 4; "mesenteric and lumbar glands all healthy" in 1; "of normal size and consistency" in 1 (cases reported by White, Axtell, Roosevelt, Musser, Smith, Fischel, Gottlieb, Sasaki). The positive findings are as follows:

In 2 cases reported by Kahler (1880) the mesenteric glands were somewhat enlarged, appearing as red bodies in the mesenteric fat; in another case they were described as red. Smith (1880) reported enlargement of the bronchial glands. In 1 case, reported by Starr, the mesenteric glands appeared smaller than usual. In the thirty-eighth case, reported by Hobson, "large lymphatics in posterior mediastinum pressing on right vagus, thoracic duct, and splanchnics. Glands in neck and axilla much enlarged." In the forty-fifth case the mesenteric glands were very large and Peyer's patches marked.

Müller (1889), in 1 case of bothriocephalus anemia the retroperitoneal glands showed medullary swelling, and the jugular lymph glands were very rich in blood resembling the spleen. In 2 cases with syphilitic history the lymph glands, especially the jugular

showed inflammation, reddening, and hyperplasia of follicles. In a case of Holt (1891) the "mesenteric glands were enlarged, not cheesy. The liver showed collections of spheroidal cells, presumably hyperplastic lymph nodes of Arnold."

White (1890) reports 1 case with enlargement of mesenteric glands and Peyer's patches; Klein 1 case in which the right cervical and inguinal glands, and especially the left cervical, were enlarged, grayish-red or grayish-yellow. In the left axilla two glands, the size of beans, were present.

In a case of Hills (1898) caseating tubercles were found in the axillary and mediastinal glands. No enlarged glands in the abdominal or inguinal regions. Nammack (1900), a case in which the "axillary lymph nodes were enlarged, peribronchial lymph nodes enlarged and anthracotic." In a case reported by Henry, in the same year, tuberculosis of mesenteric and retroperitoneal glands, without tuberculosis elsewhere, was observed. Grawitz (1901) reported 1 case in which the mesenteric glands were greatly swollen.

Eliminating accidental or coincident processes, such as tuberculosis, lymphadenitis, etc., the number of reported cases in which the lymph glands showed changes that might be regarded as belonging to the pathology of pernicious anemia becomes very small indeed. This paucity of observations may be explained by the assumption that lymph-gland changes are of very rare occurrence in this disease, or that the changes are of such a nature as to easily escape observation at autopsy, or that in many cases no adequate examination of the lymph glands has been made. It is very probable that both of the last assumptions constitute the true explanation. In the absence of any marked changes it is very likely that in many, if not the majority, of autopsy cases of pernicious anemia in which no mention is made of the lymph glands, these were either superficially examined or entirely overlooked. I am led to this conclusion by my own experience. In every one of the eight autopsy cases of pernicious anemia the prevertebral lymph glands, particularly the hemolymph nodes (cervical, thoracic, or retroperitoneal), showed changes, either gross or microscopic, which might be regarded as belonging to the essential pathology of the disease. In only one of these cases, however, were the gross changes so marked as to be noticeable without special examination of the retroperitoneal glands. Such special dissection is usu-

ally not a part of the ordinary autopsy technique. In my cases particular attention was paid to the lymph glands of all regions, for the purpose of collecting statistics of the relative occurrence of hemolymph glands in the human body.

The cases whose reports follow were from Dr. Dock's Clinic of Internal Medicine in the University Hospital, and I am indebted to the records of this clinic for the case-histories and the blood examinations.

CASE I.—O. N. R., aged fifty-four years, American parentage, salesman by occupation, was admitted to the medical clinic May 26, 1898. Family history good. Previous history negative. Had usual diseases of childhood, and an attack of typhoid fever at the age of thirty-four years. No history of venereal disease.

During the last three years he has had gaseous eructations, heartburn, and persistent constipation. For the last three months has been troubled with piles. He has noticed blood at nearly every stool, but has never lost any large amount at any one time. In December, 1897, he first noticed a gradually increasing paleness, and at the same time began to be troubled with dyspnea, palpitation, and general weakness. These symptoms are gradually becoming more marked.

Physical examination at time of admission: The patient is five feet eight inches tall, his weight 132 pounds. (One year ago he weighed 143 pounds.) Very cachectic and emaciated. Mind clear. Muscles very small and soft; panniculus very thin; marked edema at ankles. Skin is pale, sallow, with yellowish tint. Nails very pale. Mucous membranes and tongue very pale, connective tissue under tongue yellowish. Scleræ yellowish. Examination of lungs is negative. There is no apex-beat, the heart dulness is not enlarged. Heart sounds impure; pulse 88, dicrotic, regular. Examination of abdomen negative. Rectal examination showed a number of deeply congested papillomatous masses, about three-quarters of an inch in diameter, on the rectal wall just above the internal sphincter.

Blood Examination. Red blood-cells, 960,000; leukocytes, 5672; Hemoglobin, 20 per cent.; specific gravity, 1027. The red cells show a marked degree of poikilocytosis. Differential count: normoblasts, 3; megaloblasts, 5; polymorphonuclear leukocytes, 70; large lymphocytes, 7; small lymphocytes, 32.

Urine. Small amount, clear, dark reddish. Chemical tests negative. On June 2, 1898, the patient was operated upon for hemorrhoids. After the operation all traces of blood disappeared from the stools and patient became somewhat less yellow, but remained extremely pale. At the same time the number of megaloblasts became diminished. His general condition improved; there was less edema. He was discharged on June 27th, with advice to continue treatment of iron, arsenic, and hydrochloric acid, and to return later.

He was readmitted on January 6, 1900. For four or five months after leaving the hospital in June, 1898, he remained in bed, getting up at short intervals. During this time he gained in strength, but was troubled with profuse sweating and swelling of the legs. Gastrointestinal symptoms were marked. In October, 1898, he went to Texas for three months. There he continued to gain in strength, but at no time was he able to be up long. Breathlessness and palpitation continued. After his return, up to the fall of 1899, he remained about the same. At this time he began to grow weaker, and the symptoms of shortness of breath, palpitation, etc., increased, with severe pain in heart region on slight exertion. Has irregular elevation of temperature. During the last six months he has noticed a gradual pigmentation of his body, first on his arms and over the inner surfaces of thighs, and gradually appearing over the greater portion of his skin. Some of the areas have grown pale, while others have deepened in color. He has had no loss of blood from any part of the body. He has continued his treatment of iron, arsenic, etc., up to within a few weeks. The physical examination showed a marked melanoderma of face, neck, back, thorax, buttocks, elbows, pubic region, inner surface of thighs, knees, and ankles, the pigmented patches being arranged somewhat symmetrically with lighter vitiliginous areas between. (A fuller report of the condition of vitiligo shown by this case will be made elsewhere.) Otherwise the physical signs were about as before. The blood examination, made on January 7th: Blood thin, watery, and coagulates slowly. Marked poikilocytosis. One nucleated red cell (degenerating normoblast) to 150 leukocytes. Red blood cells, 874,400; leukocytes, 2546; hemoglobin, 25 per cent.; specific gravity, 1029.

The patient's condition became worse quickly. On the 8th small hemorrhagic spots appeared over the thorax and extremities. On the 10th his dyspnea and sweating had increased, there were moist râles over both lungs, mind clouded, pulse very rapid, low tension. Died at 9.03 A.M., January 10, 1900.

Clinical Diagnosis. Progressive pernicious anemia, vitiligo.

Autopsy, held January 10th, 11.30 A.M., by Dr. Warthin. Body well built, 171 centimeters long. Muscles small, emaciated, very flabby; on section pale, brownish-red, moist. Panniculus in small amount; on section bright golden-yellow. Slight edema over lower extremities. Skin over the greater portion of the body is pale, slightly scaly, and inelastic. Over the lower part of femurs, patellas, flexor surfaces of both knees, over the penis, inner surfaces of thighs, flexor surfaces of thighs and arms, over buttocks, shoulders, and thorax there are irregular patches of brown pigmentation, arranged somewhat symmetrically. Alternating with these there are areas of lighter, smoother skin. In the majority of patches there is an abrupt change from the pigment to the light areas, the edge of the pigmented portion just next to the light skin appearing much darker. The pigmented patches have a concave margin toward the light areas. In a few places there is an intermediate lighter zone between the darkest pigmentation and the white skin.

Over the legs and trunk there are sparsely scattered ecchymoses varying in size from a pinpoint to half a pea. Hair is scanty and white over head and face. The body hair is entirely absent over the white areas.

Brain and spinal cord very anemic, otherwise negative.

Diaphragm at fifth rib right and left. Mediastinal fat in large amount, bright yellow. Small amount of clear fluid in each pleural cavity. On the right side there are numerous small ecchymoses in the parietal pleura. Apex in fifth intercostal space, inside the nipple line. One hundred and fifty cubic centimeters of clear fluid in the pericardial sac. Pericardium negative. Large, irregular, tendinous spots on anterior and posterior walls of right ventricle. Heart weighs 416 grams. Subpericardial fat increased, edematous. Numerous small ecchymoses beneath the epicardium of auricles. Auricles filled with thin watery blood; no clots. Ventricles not dilated. Left ventricle hypertrophic, cavity small, the papillary muscles hypertrophic, and the chordæ tendinæ thickened. Throughout the myocardium there are small fibroid areas. Tricuspid and mitral rings slightly thickened; mitral flaps thickened and slightly retracted. Aortic valves slightly thickened, edges recurved. Pulmonary valves negative. Arteriosclerosis in the beginning of aorta. Coronary vessels sclerotic and calcified.

The left lung is free throughout, voluminous, especially lower lobe. Visceral pleura smooth, moist, clear, shining. Beneath it are about a dozen firm elevations, size of a pea, heavily pigmented, and on section show calcification. Apex is slightly retracted. Several small, airless areas felt throughout the lung. On section the upper lobe is pale gray, anthracosis moderate. Pressure yields an abundant foamy exudate. Lower lobe shows marked hypostasis. Foamy exudate without pressure. The right lung is free, except at apex, where there are many small, irregular adhesions containing adipose tissue, and not so voluminous as the left. Slight hypostasis in lower lobe. Pleura smooth, clear, and shining; contains a few calcified nodules, size of pea. Apex slightly retracted; contains small caseating tubercle and a number of smaller non-caseating nodules. Cut surface yields abundant exudate on slight pressure, but edema is not so marked as in the left lung. Pulmonary vessels negative. Bronchi contain grayish-yellow fluid. Bronchial glands heavily pigmented, contain small calcified nodules.

Thoracic aorta shows patches of sclerosis, not longitudinally arranged. Thoracic duct negative. Esophagus contains small amount of yellowish foamy mucus; mucosa pale. Mucosa of mouth and upper respiratory tract very pale. Thyroid small; on section negative. Cervical lymph glands not enlarged, but the majority heavily pigmented, deep brown.

No fluid in peritoneal cavity. Omentum rich in fat. Spleen weighs 224 grams, 12 cm. long, 8 cm. broad, 4 cm. thick. Capsule irregularly thickened; shows numerous hyaline, pearly, nodular thickenings. On section is pale brownish-red, stroma greatly increased, pulp decreased, soft, follicles not visible. Bleeds freely, vessels contain thin watery blood.

Left adrenal measures 5.5 cm. by 2.5 cm. by 2 mm.; right, 4.5 cm. by 2.5 cm.

by 2 mm.; the periadrenal tissue shows no inflammatory thickening. Blood-vessels and plexus on both sides apparently normal. No inflammatory tissue about semilunar ganglia. On section, adrenals show beginning post-mortem change in lower portions of medulla, the medullary substance in the upper part of both organs being grayish-white, firm, and showing no brown pigmentation.

The left kidney weighs 192 gm., measures 11 by 6.5 by 2.5 cm.; the right one weighs 176 gm., and measures 11.5 by 5 by 3 cm. Fatty capsule of both kidneys well developed; fibrous capsule strips off easily. Surface slightly granular. On section both kidneys are pale brownish-red, firm. Medullary pyramids pale. Cortex of left measures 6 mm., of right, 8 mm. Pelvic fat in large amount. Mucosa of pelvis negative. Ureters negative. Wall of bladder thickened, muscle trabeculæ hypertrophic. Small hemorrhage at base of bladder.

Stomach contains 300 c.c. of greenish-yellow fluid, with much whitish mucus. Mucosa covered with grayish mucus. In mucosa there are numerous ecchymoses of small size. Mucosa atrophic. Pylorus negative. No postmortem change in stomach mucosa. Intestine contains soft bile-stained fecal material. Mucosa swollen, very pale, containing small punctate hemorrhages. Numerous enlarged solitary follicles in ileum. Large intestine contains soft, pale-yellowish feces. Mucosa very pale, containing small hemorrhagic spots, and small areas of pigmentation. No free blood in any portion of the intestinal lumen. Small hemorrhoid just within the anus.

The liver weighs 1728 gm.; its greatest dimensions 25 by 17 by 7 cm. Surface is granular, capsule thickened, especially about the ligaments and near the gall-bladder. On section the surface is granular, slightly elevated, cloudy and of a pale-red chocolate color. Slight fatty smear on knife. Outlines of lobules distinct; central vein a small red point. Glisson's capsule slightly increased. Bile-ducts dilated, filled with golden-yellow bile. On the under surface of liver is a small triangular anomalous lobe of liver tissue entirely separated from the tissue of main organ by connective tissue. Its capsule is thickened, and shows lines of contraction. Gall-bladder and bile-vessels negative. Portal vein is also negative.

The pancreas weighs 136 gm., its dimensions are 24 by 4.5 by 1.5 cm. Tail is unusually thick. On section lobes are clearly outlined, interlobular connective tissue increased. Consistency normal. The splenic artery and branches are very sclerotic.

The mesentery is very rich in fat, its glands slightly enlarged, on section pale pink. The retroperitoneal glands are also enlarged, and are heavily pigmented, brownish-red in color. The glands at the brim of the pelvis in particular show this change. Hemolymph glands enlarged, brownish-red.

The prostate shows bilateral enlargement; the testicles, slight fibroid change, otherwise genitals are negative.

Bone-marrow: Red marrow deep red in color. The fatty marrow of the

long bones contains dark, reddish areas, looking somewhat like blood clots. The peripheral lymph glands are very slightly enlarged, all more or less pigmented. Near the solar plexus a number of enlarged Pacinian corpuscles are found, having pearly centers and a clear periphery.

Microscopic Examination. *Lung* shows anemia and marked edema. Old and fresh hemorrhagic infarcts. Mucopurulent bronchitis. Healed tubercles.

Heart. Atrophy and hypertrophy. Fatty infiltration and degeneration.

Spleen. Atrophy, increase of fine stroma, chronic congestion. Contains very little hemosiderin.

Kidneys. Anemic, atrophy of cortex, with localized areas of connective-tissue increase. Numerous obliterated glomeruli. Cells of convoluted tubercles show cloudy swelling, and contain a diffuse yellowish pigment which gives the iron reaction.

Liver. Atrophy, increase of connective tissue, slight fatty infiltration and degeneration, chronic congestion. Liver cells heavily pigmented with brownish pigment, most marked at the periphery of the lobule. The pigment gives the iron reaction.

Pancreas. Atrophy and increase of interlobular tissue. Some of the areas of Langerhans appear enlarged.

Adrenals. Slight atrophy and marked hemosiderosis. Collections of deeply-staining small round cells found throughout both organs; numerous mast cells present. *Stomach.* Chronic atrophic gastritis, small hemorrhages in submucosa.

Intestine. Subacute enteritis and colitis. Solitary follicles and Peyer's patches enlarged and edematous, some hemorrhagic.

Prostate. Adenomatous hyperplasia, numerous corpora amylacea.

Aorta. Marked sclerosis.

Skin. Melanoderma and vitiligo. Pigment does not give the iron reaction. (The vitiligo of this case will be reported elsewhere.)

Bone-marrow. Red marrow contains increased number of nucleated reds, and many megaloblasts. The red areas in fatty marrow are localized areas of congestion and hemorrhage.

Hemolymph Glands. (See below.) *Lymph glands.* All lymphatic glands show hemosiderosis.

Pathologic Diagnosis. Pernicious anemia, hemosiderosis of liver, kidneys, lymph glands, adrenals and spleen, vitiligo, chronic atrophic gastritis, acute enterocolitis, multiple punctiform ecchymoses, general atrophy, arteriosclerosis, healed tubercles of lungs and bronchial glands, small-celled infiltration of adrenals, hypertrophy of prostate.

CASE II.—Miss Sarah M., American, aged fifty-two years, housekeeper by occupation, was admitted to the medical clinic January 12, 1899. The patient came to the hospital because of shortness of breath, "jumping sensation" in heart region, and general weakness. Her father died at the age of sixty-five years of a disease which patient thinks was similar to hers. Otherwise family history is unimportant. Patient had usual diseases of child-

hood. There is a strong suspicion of syphilis. She has worked very hard, habits of eating have been very irregular. Menopause established three years ago. At that time she began to have pain and throbbing in epigastrium after meals, and shortness of breath developed at same time. Large "swellings" appeared on face, lasting six to eight months. Her physician at this time said that her liver and spleen were very much enlarged. She improved under treatment, but six months later became much worse, being confined to her bed for about four weeks. During this attack she several times after meals vomited a bloody-looking material which she described as "thick livery matter." Four weeks ago the throbbing pain in heart region and shortness of breath became much worse. She has been unable to sit up; mind not clear. During these attacks her skin is of a yellow color. During last summer she gained forty to fifty pounds.

Physical Examination (January 13, 1899): Patient appears very ill, cachectic, mind clouded, very restless, face swollen. Skin is very pale, sallow, inelastic. Slight edema at ankles. No enlarged glands. Examination of lungs negative. Apex in fifth intercostal space, outside of nipple line, heavy impulse, with systolic thrill. Dulness enlarged to the left nipple line and to the right one finger's breadth beyond the right edge of sternum. Loud blowing systolic murmur over the entire cardiac region, loudest over the apex, and transmitted into the axilla. Second sounds weak. Pulse, 112; low tension, somewhat dicrotic, irregular in volume and rhythm. Abdomen above level of ribs. Traube's space dull, lower border of stomach two inches above the umbilicus. Liver dulness reaches to edge of ribs. Liver is palpable. Splenic dulness begins on eighth rib, extends to edge of ribs. Spleen easily felt 1½ inches beyond the edge of ribs.

Blood Examination (January 13, 1899). Red blood cells, 888,000; leukocytes, 4700; hemoglobin, 35 to 40 per cent. *Differential count* (January 18, 1899): Small lymphocytes, 33 per cent.; large lymphocytes, 7 per cent.; transitionals, 1.8 per cent.; polynuclears, 56.2 per cent.; eosinophiles, 0.7 per cent.; degenerating leukocytes, 2.1 per cent. The red blood cells are large, as a rule, some microcytes, marked poikilocytosis. Cells are pale with large clear centers. Normoblasts, degenerating normoblasts and megaloblasts are present.

There is a trace of albumin in the urine.

The patient failed very rapidly after admission, general weakness increased, irregular fever, heart gradually became weaker, edema of legs increased, Died at 10 A.M., January 20, 1899.

Clinical Diagnosis: Pernicious anemia, dilatation of heart, relative mitral insufficiency.

Autopsy by Dr. Warthin, 11 A.M., January 20, 1899.

Autopsy Protocol. Body well built, 159 cm. long. Muscles very soft and flabby, rigor mortis present only in muscles of jaw. Body heat present over trunk. Panniculus very thin, on section orange-yellow. Moderate edema over lower extremities, slight edema over the remainder of the body. Skin

pale sallow with yellowish tint; numerous small pigmented patches over both legs. Small ecchymosis in abdominal wall, just below umbilicus. Small patch of ectatic veins on outer surface of right thigh. Slight hypostasis over back. Brain negative, except for anemia and slight sclerosis of cerebral vessels. Spinal cord not examined.

Diaphragm on right at third interspace, on left at fifth rib. Left mammary gland is negative, right one contains small cyst. Position of thoracic organs negative, except for apex of heart, which is in the fifth interspace in the anterior axillary line. Mediastinal fat abundant, bright-yellow and moist. No remains of thymus.

Pericardial sac contains 100 c.c. of clear fluid. Pericardium pale, clear, shining. Large tendinous spot on anterior wall, and smaller one on posterior. Heart weight 473 gm., and is three times the size of cadaver's right fist. Subepicardial fat is increased, beneath the epicardium there are numerous punctiform hemorrhages, the largest being at the apex. The apex is formed by the left ventricle. The right auricle is greatly distended, the muscle fibers separated. Right heart filled with thin watery blood, no clots. Left side not dilated. Left ventricular wall measures 10 to 15 mm., right, 2 to 5 mm. Mitral orifice barely admits two fingers, flaps thickened, posterior one shortened. Aortic flaps thickened, but adequate. Punctiform hemorrhages beneath endocardium. Heart muscle pale yellowish-brown, soft. No sclerosis in aorta.

Both lungs moderately collapsed, very pale; moderate anthracosis, moderate edema. Small calcified nodules in upper lobe of left. Bronchi, bronchial glands and pulmonary vessels negative. Upper respiratory tract negative, except for extreme paleness of mucous membranes. Tonsil contains a number of small scars. Small hemorrhage on upper surface of right vocal cord. Both lobes of thyroid enlarged, in the left lobe there is an adenoma, size of small pigeon's egg. Esophagus, trachea, and thoracic duct negative. Cervical lymph glands enlarged, some of them showing anthracosis.

No fluid in peritoneal cavity. Position of abdominal organs negative. Omentum rich in fat, contains three small firm pinkish bodies, the largest, size of a bean.

The spleen weighs 570 gm., and measures 18.5 by 9 by 5.5 cm.; about three times normal size; edges thick and rounded. Capsule tense, thickened, and opaque. Cut surface is dark red, consistence firm, stroma increased, follicles enlarged, bleeds very little. Splenic vessels show marked sclerosis.

Adrenals negative; no postmortem change.

Left kidney weighs 160 gm., and measures 12 by 4.5 by 4 cm. Right kidney weighs 146 gm., and measures 12 by 5 by 4 cm. Cortex of left kidney 0.5 cm. broad; that of right a little less. Fatty capsule of both kidneys very large; fibrous capsule thickened and slightly adherent. Surface granular; that of the right more so than the left. Cut surface is pale brownish-red, slightly granular, consistency increased. Small grayish areas in cortex;

waxy shine; glomeruli plainly visible; pelves and ureters negative; bladder distended with clear urine; wall thin and pale. Stomach shows no post-mortem change; no atrophy or other pathologic change; contains about 500 c.c. of greenish fluid, in which there is a whitish powder. Intestines filled with soft, greenish, fecal material. Mucosa pale; otherwise entirely negative. Appendix normal.

Liver weighs 2105 gm., and measures 30 by 23 by 10 cm. Lower edge is three fingers' breadth below edge of ribs in right nipple line. Left lobe is lengthened and flattened; on its upper surface is a depression corresponding to the position of the heart. Numerous adhesions over the anterior surface. Capsule thickened, especially near the ligaments. On section the organ is brownish-yellow; lobules not clearly defined; very little blood in veins. Slight, fatty smear on knife. Consistence increased. Gall-bladder distended, filled with dark-brown, glairy bile, wall thin; bile passages and portal vein negative.

Pancreas large; marked fatty infiltration; vessels sclerotic. Three enlarged glands behind pancreas; on section pinkish-brown. The mesentery is very rich in fat; the mesenteric glands not enlarged. The retroperitoneal glands are not enlarged; many of them are pinkish or brownish in color. The abdominal aorta shows a moderate degree of sclerosis.

External genitals negative; vagina negative; cystic polypoid growth on cervix; cystic endometritis; uterine wall atrophic. Left tube twisted, bent upon itself, surrounded by many adhesions; few adhesions about right tube. Ovaries atrophic, the left one bound down by adhesions. Uterine ligaments thickened; show many adhesions, also adhesions between uterus, ovaries, and rectum.

Marked osteoporosis of the long bones; the medullary canal of the right tibia about twice normal size. Marrow bright red; no fatty marrow in long bones; hyperplasia of red marrow in clavicle, etc. The peripheral lymph glands are not enlarged, negative.

Microscopic. Spleen. Fibroid hyperplasia; moderate hemosiderosis. *Liver.* Atrophy; fatty degeneration; hemosiderosis of peripheral zone of lobule; chronic endarteritis in hepatic artery. *Kidneys.* Early stage of primary contracted kidney; chronic endarteritis; hemosiderosis of convoluted tubules. *Pancreas.* Fatty infiltration. *Lungs.* Atrophy; edema. *Heart.* Atrophy; fatty degeneration and infiltration. *Adenoma of Thyroid.* Adenoma showing large myxomatous areas partly infiltrated with red blood cells. *Stomach and Intestines.* Negative. *Bodies from Omentum.* Hemolymph glands showing pigmentation and active hemolysis. *Bone-marrow.* Fatty marrow transformed to lymphoid marrow containing many nucleated red cells. *Retroperitoneal Glands.* (See below.)

Pathologic Diagnosis. Pernicious anemia; hemosiderosis of liver, spleen, kidneys, and hemolymph glands; hyperplasia of lymphoid marrow; fibroid hyperplasia of spleen; general atrophy; fatty infiltration and degeneration of heart; cardiac dilatation; mitral insufficiency.

CASE III.—Mrs. H. E., aged fifty-eight years, American, housewife, was admitted to the medical clinic November 24, 1900. Patient comes to hospital for general weakness, shortness of breath, and frequent hemorrhages from nose, gums, and bowels.

Family history negative. Previous history good. Has always been a very hard worker. Menopause began at forty-three years of age; flowed excessively at intervals up to the age of fifty-one years, when flow suddenly ceased. The present trouble began a year from last August, when she contracted a severe cold, became very constipated and weak. Two months later she fell and struck her forehead. Six days later she had a severe epistaxis, lasting six hours. A month later had another attack of epistaxis of eight hours' duration. Periodical attacks of nose-bleeding occurred every month until the following spring, the epistaxis continuing from seven to ten hours without apparent ill effects. For seven weeks previous to last May was free from hemorrhage, but in May began to have hemorrhages from nose and gums, continuing more or less for six weeks. During the greater part of this time she was confined to her bed, extremely weak, nauseated, and retained food with great difficulty. In July she had an epistaxis of thirty-six hours' duration; slight one during August. In September had another severe attack, and vomited a great deal of blood. Cannot say whether blood came from stomach or nose. During the middle of October had almost constant though not profuse hemorrhages from nose, gums, and lips. During the last two weeks these have ceased, but she has had a bloody diarrhea, the blood coming in a steady stream at times and apparently unchanged. During the periods of hemorrhage she is very weak, staggers in walking, but has lost consciousness only once. Elastic swellings have appeared in various parts of her body, the first and largest, the size of two fists, on the right shoulder, gradually working down the right side to the right hip, where it ultimately disappeared. A similar mass on the left arm became harder. The skin over the abdomen became discolored, the discolorization rapidly disappearing. Sight has become dim; appetite remains good; has lost fifty pounds; irregular fever.

On December 7th patient became comatose, but could be aroused easily. Face was very edematous; marked edema at ankles. Pulse 110; low tension. Later in the day the coma deepened, breathing more labored. Died suddenly at 5 A.M., December 8th.

Blood Examination. Red blood cells, 1,280,000; leukocytes, 3000 to 4000; hemoglobin, 20 per cent.

The differential count of 500 leukocytes showed: Small lymphocytes, 40.4; large lymphocytes, 3.3; transitionals, 2.2; polynuclears, 53.6; eosinophiles, 0.4; degenerating leukocytes, 0.2 per cent.; one normoblast in two smears. (Smears given to blood class in Pathologic Laboratory showed in some covers from two to three megaloblasts and same number of degenerating normoblasts.) The blood showed evidences of an extreme active hemolysis. The red cells were nearly all round, some dark, many pale or shadowy.

The plasma showed a tendency to stain around the red cells. The red cells are grouped two or three or more in a bunch. No particular change in the leukocytes.

Clinical Diagnosis. Anemia (active hemolysis); hemophilia.

Autopsy performed by Dr. Warthin at 11.45 A.M., December 8th, at undertaking shop.

Autopsy Protocol. Body five feet six and a half inches tall, well built; abdomen distended above the level of the ribs, punctured by undertaker. Muscles small and flabby; on section very pale and soft. Rigor mortis present throughout, Panniculus in fair amount; on section orange-yellow, moist. Skin dry, inelastic, pale, sallow, with yellow tint. Numerous small pigmented nævi scattered over the body. Several angiectatic areas or subcutaneous hemorrhages. Over the forearm, face, neck, external genitalia, and knees the skin is moderately pigmented, the pigmentation less marked over the flexor surfaces. Mucous membranes pale yellow; scleræ very slightly yellow; pale hypostasis over back; hair of scalp abundant, grayish; marked edema over lower extremities, slight over thorax; body heat absent.

Head and spinal cord not examined.

Diaphragm, fifth rib on right, sixth intercostal space on left. Mammæ atrophic. Position of thoracic organs normal; mediastinum negative; thymus fat in small amount; pleural cavities filled with fluid smelling of undertaker's injection; pleuræ negative; pericardium negative. Heart larger than right fist; weighs 186 grams. Small tendinous spot on posterior wall of right ventricle; no subepicardial ecchymoses. On section heart muscle is pale brownish-red in color; subepicardial fat greatly increased. Left ventricle wall 12 mm. thick, right 5 mm. Valve flaps and orifices negative. Both lungs entirely free, the right one partly collapsed, the left more voluminous. Pleuræ negative. On section both lungs are pale pinkish-gray in color; yield abundant foamy exudate on slight pressure; emphysematous along edges and at apices. Pulmonary vessels negative; bronchi empty; mucosa pale; bronchial glands moderately enlarged, moderately pigmented. Arch of the aorta and thoracic aorta show beginning arteriosclerosis. Upper respiratory tract negative. Thyroid enlarged; contains hyaline and calcified areas. Cyst, size of a cherry, in the lower part of the left lobe. Thoracic duct negative; esophagus negative.

Liver two hand breadths below the ensiform and a hand breadth below the edge of ribs; otherwise position of abdominal organs is negative. The omentum is rich in fat, rolled up at the level of the umbilicus. Peritoneum negative. In the serosa of the small intestine there is a number of small hyaline thickenings. No fluid in peritoneal cavity.

Spleen weighs 208 grams, about normal in size and shape; notches on anterior margin well marked. Capsule slightly thickened and wrinkled; consistency soft. On section pulp is bluish-red, stroma slightly increased; follicles somewhat diminished in number, but of fair size.

The adrenals show postmortem change, otherwise negative.

The left kidney weighs 240 grams. Fatty capsule well developed. Kidney more plump than normal. Fibrous capsule thickened and slightly adherent. Numerous retention cysts in surface of cortex, varying in size from a pinhead to a pea. On section the surface is slightly granular, pale, firmer, and more translucent than normal. Labyrinth and medullary rays not well marked. Glomeruli not easily seen. Cortex measures from ½ to 1 cm. Pelvic fat increased. The right kidney weighs 256 grams, similar to left, except that the lower pole is almost entirely replaced by a large retention cyst having a clear wall, almost transparent, and containing clear fluid. In upper pole there are other similar cysts of the size of a cherry. Both ureters dilated, left more than right. Mucosa pale, otherwise negative. Bladder greatly distended; wall smooth.

Stomach contains food remains and small amount of mucus. Mucosa swollen; no evidences of atrophy. Mucosa of small intestine very pale, otherwise no change. Neither the solitary follicles nor Peyer's patches enlarged. Appendix long, slender; has long mesentery, very rich in fat. No adhesions. Cecum moderately dilated. Ascending colon contains pale-yellowish, unformed feces. Mucosa shows little change. Transverse colon is contracted, mucosa covered with tenacious mucus and small fecal lumps; no evidences of hemorrhage. Descending colon empty. Mucosa covered with large amount of mucus. Mucosa pale, thickened; no evidences of hemorrhage. Above the anus there is a ring of large, dark-blue, tortuous hemorrhoids. No evidences of recent hemorrhage from these.

The liver weighs 1920 grams, much flattened, its sagittal diameter increased. Over the lower border of the right lobe corresponding to the edge of the ribs there are two shallow furrows, from 1 to two fingers' breadth in width, over which the capsule is much thickened and opaque. The surface of liver is more or less irregular, especially that of the left lobe and the under surface of the right one. Capsule is thickened throughout; more marked thickening over the depressions and furrows. Consistency decreased. On section shows a well-marked nutmeg appearance, central portion of lobules deep red, peripheral brownish-yellow. Marked fatty smear. Gall-bladder filled with dark golden-brown bile; mucosa negative; wall somewhat edematous; bile passages patent.

Pancreas very small, flattened; consistency decreased. On section, lobules small and pale. Fat about pancreas in large amount. No hemorrhage. Portal vein negative. Mesenteric glands not enlarged. Retroperitoneal lymph glands enormously enlarged, forming large, flattened masses lying along the vessels, on both sides of the spinal column from the bifurcation of the common iliacs to the solar plexus. Enlargement more marked on the right side than on left. Glands around the solar plexus very large and firm. The glands are partly dark red, partly pale, showing a number of dark red areas; consistency soft, cut surface somewhat granular; the scraping yields a large number of cells. Vessels greatly dilated and filled with thin blood.

The external genitals are pale, labia somewhat edematous; cervical

ectropion. Uterus enlarged, thick, irregular increase in size, due to a number of myofibromata in wall, from size of cherry to walnut. The tubes atrophic; ovaries small and atrophic, show many hyaline scars. The right ligament is studded with numerous small hyaline bodies, the majority translucent and slightly yellow. Some are firm, others cystic; vary in size from pinhead to small pea.

Red marrow, dark red. Long bones show marked osteoporosis, the medullary canal greatly enlarged, the fatty marrow replaced by dark red to almost black lymphoid (?) marrow containing small cysts filled with dark-red fluid blood. The firm portion of the bone forms a very thin shell around the canal, and is much softer than normal. Peripheral lymph glands not enlarged.

Microscopic. Heart shows marked atrophy, fatty infiltration, and moderate fatty degeneration. *Lungs.* Very marked simple atrophy and emphysema, and dilatation of smaller bronchioles. *Spleen.* Atrophy and chronic congestion, moderate hemosiderosis. *Liver.* Marked chronic congestion (nutmeg liver), slight hemosiderosis of peripheral zone of lobules. *Kidneys.* Early stage of chronic interstitial nephritis, numerous retention cysts, slight hemosiderosis of convoluted tubules. *Pancreas.* Fatty atrophy, congestion, beginning postmortem change. *Stomach.* Chronic catarrhal gastritis, moderate atrophy. *Intestine.* Negative. *Ovaries.* Atrophy. *Cysts from broad ligament.* Follicular cysts lined with large flattened or cuboidal cells; contain a mucoid or firm colloid substance. *Skin.* Small hemorrhagic areas.

Bone-marrow contains many hemorrhagic areas and small scattered islands of lymphoid marrow, these being made up chiefly of lymphocytes and numerous giant cells. Cysts containing fresh blood.

Lymph Glands. See below.

Pathologic Diagnosis. Anemia gravis; active hemolysis; lymphoid hyperplasia of retroperitoneal glands (lymphosarcoma (?), infective granuloma (?), early stage of leukemia (?); lymphoid and cystic changes in bone-marrow; fatty heart; atrophy, chronic congestion of spleen, lungs, liver, etc.; early stage of chronic interstitial nephritis; myofibromata of uterus; multiple ecchymoses in skin.

CASE IV.—W. M., aged twenty-two years, American, laborer, admitted to medical clinic January 25, 1901. His family history is unknown. At twelve years of age had an attack of "jaundice" lasting two weeks; otherwise has had fair health. He entered the army service April 29, 1898, and was sent to Porto Rico, where he almost immediately contracted malaria and chronic diarrhea. Was discharged April 14, 1899. Has not been well since. Has four to five stools daily; these are thin, watery, and passed with much gas and more or less pain. He has great thirst, drinks an average of two gallons daily. Passes about one gallon of urine during the night, does not know how much during the day. Complains of great general weakness, constant pain in lumbar region, and at times swelling of extremities and face.

Physical Examination. Weight, 95¾ pounds. Very cachectic and emaciated; skin and scleræ of a muddy tint, pigmented patches over neck and spine. Examination of lungs negative. Heart sounds weak, soft blowing systolic murmur at apex. Pulse rapid, low tension. Has irregular low fever. No enlargement of spleen, liver, or lymph glands. Specific gravity of urine, 1003; chemical tests negative. Examination of stools showed no protozoa, no worms or eggs; no blood; many leukocytes.

Blood Examination. Red blood cells, 960,000; leukocytes, 3172; hemoglobin, 20 per cent.; specific gravity, 1027. Red cells show marked poikilocytosis, stain very poorly; few degenerating normoblasts.

The patient rapidly became very weak, attacks of faintness occurring. Died 8.30 A.M., January 29, 1901.

Clinical Diagnosis. Anemia; chronic diarrhea.

Autopsy by Dr. Warthin, 4 P.M., January 29, 1901.

Autopsy Protocol. Body measures 170 cm., much wasted and cachectic. Muscles emaciated, very flabby; on section, brownish-red, dry, do not tear easily. Rigor mortis present throughout. Panniculus almost entirely absent; on section, pale orange-yellow, dry. Trace of edema over lower extremities. Skin dirty sallow, marked pigmentation in axillæ, around the nipples, over abdomen, genitals, and thighs. Numerous small pigmented moles scattered over the body; pigmented patch over eighth rib, in right anterior axillary line. Very slight, pale hypostasis over back. Body heat present over abdomen and lower part of thorax. Body hair scanty, scalp hair dry and thin.

Brain and cord very anemic, otherwise negative.

Diaphragm, fourth rib on right; fifth intercostal space on left. Apex in fourth interspace, half-way between left parasternal and nipple lines. Mediastinal fat in small amount, no enlarged glands. Thymus fat in small amount, no remains of thymus. Small amount of cloudy, yellowish fluid in both pleural sacs.

Pericardial sac moderately distended; contains 75 c.c. of pale yellow, slightly cloudy fluid. Parietal pericardium negative. Epicardium clear, shining, moist; a few small ecchymoses beneath the epicardium of right auricle. Heart weighs 304 gm., size of cadaver's right fist, soft; subepicardial fat in slight excess. On section, heart muscle is pale brownish-yellow, soft, tears easily. Right auricle and vena cava distended with thin, watery blood and large yellowish agonal clot. Left auricle divided into a number of anomalous narrow lobules slightly recurved on themselves. Left ventricular wall measures 10 mm., right 3 mm. Slight thickening of proximal margins of mitral flaps, otherwise the valves and orifices are negative.

Left lung entirely free, moderately voluminous. Pleura negative. On section, lung is extremely pale, almost bloodless, slight foamy exudate obtained by pressure. Right lung free, except for a tough band of adhesion at apex containing a calcified nodule. On section, similar to left. Pul-

monary vessels negative. Mucosa of bronchi pale. In the right peribronchial glands is a number of caseous and partly calcified areas. Thoracic duct negative. Mucosa of upper respiratory tract very pale. Left tonsil enlarged; suppurating crypt. Left lobe of thyroid moderately enlarged.

In the right side of neck, along the anterior border of sternocleidomastoid and just below the angle of the jaw, there is an elastic, lobulated body, about 4 cm. long by 2 cm. wide. Skin over mass is pigmented, but freely movable; there is no external opening. On section, presents appearance of fat tissue.

Small amount of clear yellow fluid in peritoneal cavity. Omentum contains small amount of fat, very anemic, lower edge rolled to level of umbilicus. Intestines uniformly distended, walls thin, dry, bloodless. Sigmoid flexure greatly distended, completely filling up the pelvis and inguinal regions. Colon also greatly distended.

Spleen weighs 240 gm., somewhat enlarged, flattened, soft. Anterior notches small. Near the upper pole there is a deep posterior notch. Capsule is slightly wrinkled. On section, pulp is swollen, covering up the stroma, mottled pale red and darker red. Follicles easily seen.

Adrenals negative. Left kidney weighs 296 gm., right 240 gm. Fatty capsule of both rather poor in fat, fibrous capsules slightly adherent. Both kidneys plumper than normal, surfaces slightly granular, consistency increased. On section, parenchyma very pale and firm; outline of labyrinths and medullary rays not distinct, glomeruli barely visible. Medullary pyramids pale, glistening, almost white. Iodine test for amyloid negative. Pelvis dilated. Ureters greatly dilated. Bladder enormously distended, filled with pale urine. Mucosa pale, smooth.

Mucosa of stomach very pale, otherwise negative. In the ileum there are scattered erosions over enlarged solitary follicles. These increase in number and size toward the ileocecal valve. In Peyer's patches are several small ulcers, the largest 15 mm. long and 5 mm. wide. Ulcers are excavated, have overhanging thickened margins, base covered with gray exudate, do not extend through the submucosa, are longitudinal, and not circular. Serosa shows no change. No ulcers in colon. Rectum negative.

Liver weighs 1792 gm.; rounder than normal, capsule negative. On section, color pale yellowish-brown, central veins congested, pale red. Surface cloudy, slight fatty shine and smear. Gall-bladder contains pale golden-yellow bile, negative. Bile passages normal.

Pancreas extremely pale, outlines of lobules sharply marked.

Mesenteric glands moderately enlarged. On section, pale, homogeneous; no necrosis.

Retroperitoneal hemolymph glands greatly enlarged, especially on the right side of spine behind the vena cava, along the abdominal aorta, and near the left renal artery. Glands are of a deep-brown color. Glands about solar plexus also enlarged and of brown color, though not so dark as the hemolymph glands.

With the exception of a large varicocele on left side, and thickening of the testicular tunics, genitals are negative.

Bone-marrow. Red marrow bright red; fatty marrow pale, shows no lymphoid areas in long bones of lower extremities.

Peripheral lymph glands negative.

Microscopic. Heart. Simple atrophy. *Lung.* Atrophy, hemorrhagic infarction. *Bronchial glands.* Old calcified tubercles. *Tonsils.* Chronic tonsillitis. *Tumor from neck.* Lipoma. *Liver.* Simple atrophy, slight fatty change, slight hemosiderosis of peripheral zone of lobule. *Spleen.* Congestion, hyperplasia of pulp. *Kidneys.* Atrophy, dilatation of tubules, slight hemosiderosis of cells of convoluted tubules. *Adrenals, pancreas,* and *thyroid* negative. *Intestinal ulcers.* Tuberculous (?). *Mesenteric glands.* One gland containing a number of tubercles showing caseation and large giant cells.

Hemolymph and Retroperitoneal Glands. See below.

Bone-marrow. Red marrow shows great number of normoblasts and megaloblasts. Fatty marrow shows no lymphoid change.

Pathologic Diagnosis. Pernicious anemia (?); tuberculous ulcers of intestine; tuberculosis of mesenteric and bronchial glands; acute congestion of spleen; general marasmus and atrophy of all organs; lipoma of neck.

CASE V.—O. D. C., aged twenty-five years, American, farmer, admitted to medical clinic January 20, 1901. Comes to hospital because of diarrhea, gastric disturbances, shortness of breath, and yellowness of skin. Family history negative. Had frequent "fits" when a baby. Was not strong as a boy; had several attacks of vomiting. Habits good. In February, 1898, had an attack of "grippe," since which time he has not been well. Has had frequent attacks of nausea and pain in stomach, in which he vomits; is better after vomiting. Under treatment with arsenic he became better, but is at present so weak that walking is fatiguing. Is troubled with palpitation. Has from two to three loose, watery stools a day; no blood in stools. Of late this condition has been improving. During attacks has sore mouth, fever, frontal headache, and feeling of numbness over entire body. Has no appetite.

Physical Examination. Cachectic, but not emaciated; mind is clear. Muscles small and soft. Fair amount of panniculus. Skin is light yellow; mucous membranes very pale. Scleræ contain yellowish fat; no jaundice; no enlarged glands. Examination of lungs negative. No apex-beat. Heart dulness not enlarged; first sound impure. Over pulmonary area there is a short, soft blowing systolic murmur. Pulse 88, regular, of low tension. Splenic dulness enlarged, spleen not palpable. Liver dulness not enlarged. Succussion in stomach. Urine contains albumin and casts. No blood, mucus, parasites, or eggs, in stools.

Blood Examination. Red cells 1,600,000; leukocytes, 4413; hemoglobin, 35 to 40 per cent.; specific gravity, 1040. Red cells show marked poikilocytosis; no nucleated red cells found.

The patient remained in hospital until March 7th. Improved greatly; hemoglobin rose to 60 per cent.. He was allowed to take medicines (iron, hydrochoric acid, etc.) and to go home, returning in a few months for further examination.

He returned April 17th, neither looking nor feeling as well as when he left. Has increased shortness of breath, loss of appetite, irregular fever; skin is more yellow. Red cells, 1,828,000; hemoglobin, 40 per cent. From this time on he gradually grew weaker, with short periods of apparent improvement. Attacks of nausea, vomiting, and precordial pain became frequent; a number of attacks of nose-bleed occurred. Red cells and hemoglobin steadily went down, the blood count on May 3d being: Red cells, 766,000; leukocytes, 8567; hemoglobin, 35 to 40 per cent. Red cells showed marked poikilocytosis; degenerating normoblasts and megaloblasts present. Died May 15, 1901, at 4.15 A.M.

Clinical Diagnosis. Pernicious anemia.

Autopsy by Dr. Warthin, 9 A.M., May 15, 1901.

Autopsy Protocol. Body 167 cm. long; no anomalies or deformities. Abdomen below the level of the ribs. Muscles small, soft, and flabby; on section, pale brownish-red. Small amount of panniculus; on section, light lemon color. Slight edema over lower extremities. Rigor mortis present throughout. Body heat present in slight amount over thorax and abdomen. Skin and scleræ of a dirty lemon color. Genitals are heavily pigmented; darker pigmentation on under side of penis. Skin over abdomen and flexor surfaces darker than elsewhere. No hypostasis.

Inner surface of skull-cap much eroded and roughened. Dura adherent over convexity, and thicker than normal. With the exception of extreme anemia, brain and spinal cord are otherwise negative.

Diaphragm at sixth intercostal space on right, sixth rib on left. Position of thoracic organs negative. Examination of mediastinum negative. No remains of thymus. No fluid in left pleural cavity, small amount in right. Left pleura covered with small, delicate adhesions; right pleura smooth and shining. Pericardial sac distended. Pericardium negative. Subepicardial fat in excess.

Heart weighs 322 gm. Somewhat smaller than cadaver's right fist. Cavities contain pale, watery blood. Heart muscle very pale brownish-yellow, very soft, tears very easily. Thickness of left ventricular wall, 10 to 12 mm.; of right, 2 to 3 mm. of muscle, 1 to 2 mm. of fat. Slight thickening of proximal surfaces of mitral flaps; otherwise valves and orifices are normal.

The left lung weighs 490 gm. It is adherent throughout by delicate, easily torn adhesions. Voluminous. On section, extremely pale; slight hypostasis in posterior portion of lower lobe. On pressure yields an abundant foamy exudate. Very slight anthracosis. Right lung weighs 360 gm. Entirely free. Otherwise similar to left lung. Mucosa of bronchi extremely pale; they contain grayish, foamy fluid. Pulmonary vessels and bronchial

glands negative. Mucosa of esophagus very pale. Thoracic duct and great vessels of thorax negative. In the posterior mediastinum three small deep-red glands were found (hemolymph glands).

Mucous membranes of upper respiratory tract very pale; teeth very poor. Thyroid very small, weighs 20 gm. Two parathyroids on left side, one larger one on right side; all three very brown. In the deep cervical region about thirty small glands, size of pea or larger, red to deep bluish-red in color, were found (supposed hemolymph glands).

Peritoneal cavity contains one liter of clear fluid (undertaker's injection).

Liver two fingers' breadth below edge of ribs, in right nipple line. Colon is distended, lies below the level of the umbilicus. Position of abdominal organs otherwise negative. Omentum very rich in pale lemon-colored fat.

The spleen weighs 126 gm. and measures 11.5 by 7 by 3 cm. Rather flat, kidney-shaped. The poles curve anteriorly much more than normally. On the anterior edge are several deep notches, one very deep one near the upper pole. Capsule is thickened, and near the upper pole is covered with fine, stringy adhesions. On section, the pulp is a light brownish-red color, consistency firm; stroma relatively increased; follicles decreased in number and size. Very pale, watery blood in larger vessels.

The left kidney weighs 140 gm. and measures 10.5 by 5 by 3 cm. The fatty capsule is moderately rich in pale yellow fat. Fibrous capsule strips off easily. Surface very pale, venæ stellatæ barely visible. On section, the surface is very pale, moist, and shining. Pelvic fat increased. The right kidney weighs 156 gm. and measures 10 by 4 by 2.5 cm.; in all respects similar to the left. Both adrenals negative. Ureters and bladder negative.

The stomach is moderately distended. Strong odor of H_2S on opening. Contains small amount of bile-stained fluid. Wall very thin; mucosa very atrophic, covered with bile-stained mucus. Punctiform hemorrhages scattered throughout mucosa. Mucosa of duodenum very pale. About the middle of the ileum there is a small superficial ulcer apparently almost healed. Appendix negative. Large intestine contains pale, formed feces. Mucosa very pale.

The liver weighs 1736 gm.; greatest dimensions 34 by 18 by 7.5 cm. Capsule slightly thickened about the ligaments. On section, very anemic, light chocolate color. Lobules distinctly outlined; central portion of lobules paler than peripheral and slightly elevated; has "cooked" appearance. Gall-bladder adherent to duodenum and pylorus by easily torn adhesions. Distended with dark brownish bile. Bile passages patent. Portal vein negative.

Pancreas negative. Near its tail is a small body, size of pea, pale brownish color, resembling spleen.

The mesenteric glands are not enlarged, appear normal.

About fifty small glands, largest size of a bean, all red or bluish-red in color, taken from the retroperitoneal region.

Penis and scrotum deeply pigmented, testicles very small and soft; otherwise examination of genitals negative.

The peripheral lymph glands are not enlarged and present no unusual appearance. Fatty marrow of long bones contains lymphoid areas. Marked osteoporosis.

Microscopic. Heart. Atrophy and fatty degeneration. *Lungs.* Edema and a number of old hemorrhagic infarcts. *Spleen.* Atrophy, fibroid hyperplasia, chronic congestion, hyaline change in walls of vessels, very slight hemosiderosis. *Kidneys.* Marked hemosiderosis of the cells of the convoluted tubules. *Stomach.* Atrophic catarrhal gastritis. *Pancreas.* Slight atrophy. *Liver.* Atrophy and fatty degeneration, the latter process being most marked in the central portion of the lobules. Marked hemosiderosis of the peripheral zone of lobules. *Marrow.* Fatty marrow from tibia contains a few points of red marrow. *Red-marrow.* Megaloblastic in character. *Lymph glands.* No change in ordinary lymphatic glands; one gland from cervical region showed an apparent great increase in number of bloodvessels, the walls of these being greatly thickened.

Hemolymph Glands. See below.

Pathologic Diagnosis. Pernicious anemia; hemosiderosis of liver and kidneys; marked hemolysis in hemolymph glands; chronic catarrhal gastritis; fatty degeneration of heart; megaloblastic red marrow.

CASE VI.—R. C. J., aged thirty-one years, American, army service, was admitted to medical clinic, April 19, 1901. Comes to hospital for chronic diarrhea and general weakness. Family history negative. Previous history good. Present trouble began March, 1899, while with the United States Army in the Philippines. Had what was called dysentery, eight to fifteen bloody stools a day; usually in the morning he would pass about a teacupful of slime and blood, with a little fecal matter. This attack lasted a month. Since that time he has had diarrhea and vomiting. Has no pain at stool. Has lost fifty-five pounds. Has irregular fever. At times he is so weak that he is obliged to go to bed. Fainted while going from the waiting-room to the ward.

Physical Examination. Greatly emaciated; musculature very small and soft. Panniculus very thin. Skin pale sallow, with yellowish tinge. No pigmentation. Nails and mucous membranes very pale. No edema. No enlarged glands. Examination of lungs negative. No apex-beat. Heart dulness not enlarged; sounds weak, no murmurs. Pulse regular, small, low tension. Liver and spleen not enlarged, not palpable. Marked succussion in the region of the umbilicus.

Blood Examination. Red cells, 1,200,000; leukocytes, 5700; hemoglobin, 25 per cent.

Patient improved for a few days after entrance, but complained of night-sweats and sore mouth. No protozoa, worms, or eggs found in stools. On May 13th he complained of great pain from hemorrhoids. Referred on May 19th to surgical clinic for operation. Blood examination before operation

May 20th: Red cells, 850,000; leukocytes, 5602; hemoglobin, 30 per cent.; specific gravity, 1040.

On June 1st a small fistula developed near the anus, and a hard swelling appeared near this somewhat later. The patient gradually became weaker and more emaciated, pulse small and weak. Mind became clouded. On July 6th became unconscious at 9 A.M., remaining so until death at 12.45 noon.

Clinical Diagnosis. Pernicious anemia; chronic dysentery; ischiorectal abscess.

Autopsy by Dr. Warthin, 2.00 P.M., July 6, 1901.

Autopsy Protocol. Cadaver 157 cm. long, frame small. Much emaciated; muscles small; on section, brown in color, tear easily. Rigor mortis present only in muscles of jaw. Panniculus almost absent; on section, orange-yellow. Skin very pale, with light-yellow tint; no hemorrhages. Sclerotics slightly yellowish. Slight edema at ankles. Very slight hypostasis over back. No pigmentation.

Brain and spinal cord not examined. (No permission.) Diaphragm, fifth rib on right; fifth interspace on left. Position of thoracic organs normal. Mediastinal fat in small amount, no remains of thymus. No fluid in pleural cavities, no pleural adhesions.

Pericardial sac contains 20 c.c. of slightly cloudy, yellowish fluid. Pericardium normal. Heart weighs 256 gm., rather small. Epicardium somewhat opaque, subepicardial fat small in amount, fat tissue semifluid. Heart muscle reddish-brown, tears easily. Left ventricular wall 15 mm. thick; right, 2 to 5 mm. Chordæ tendinæ somewhat shortened, endocardium of left auricle thickened. Mitral orifice somewhat thickened, otherwise valves are negative. Foramen ovale is closed, but in the auricular septum there are several small communicating openings, covered by a thin membrane on the right side.

Both lungs voluminous, moderate anthracosis, upper lobes pale; lower ones dark red; on pressure yield abundant foamy exudate. In right lower lobe a small mass of calcification. Pleura entirely free, slightly thickened over the upper right lobe. Pulmonary vessels, bronchi, and bronchial glands negative. Small patches of sclerosis in aorta. Thoracic duct negative. Upper respiratory tract negative except for paleness of mucosa. Thyroids moderately enlarged; parathyroids small, brown. Cervical hemolymph glands enlarged, brownish-red in color.

About 90 c.c. of fluid in peritoneal cavity; peritoneum negative. Omentum poor in fat, rolled up, fat of a clear hyaline appearance. Position of abdominal organs normal.

Spleen weighs 96 gm., small, triangular in shape. Small notch at lower portion of the anterior margin. Capsule thickened and wrinkled. Small white pearly nodules scattered over surface. On section, stroma increased, follicles few, consistency soft, color brownish-red.

Adrenals negative, save for beginning postmortem change.

Left kidney weighs 184 gm.; right one, 176 gm. Fatty capsule of both poor in fat. Fetal lobulation of kidneys preserved to slight extent. Color deep brownish-red. A number of small hyaline nodules, size of pinhead found, in cortex of both kidneys; some of these have yellow centers. Ureters negative. Bladder greatly distended, filled with clear yellow urine.

Stomach contains about 100 c.c. of greenish-yellow fluid containing milk curds and large amount of mucus. Mucosa pale, thickened, especially toward pylorus. In the fundus are two large ulcers in process of healing and one completely healed. Mucosa covered with grayish mucus.

Intestines filled with soft, yellowish, unformed feces. Mucosa very pale; small punctiform hemorrhages in lower part of small intestine. No ulcers. Colon filled with light yellow, unformed feces. Mucosa pale, containing small punctiform hemorrhages. No ulceration. No parasites.

Liver weighs 1136 gm.; small, rather round in shape. Light chocolate color. Beneath capsule a number of small cyts, size of a pinhead to small pea. Wall of cyst thick and hyaline. No pus, no parasites found in these. On section, liver is anemic, yellowish-brown, consistence firm, lobules fairly distinct. Gall-bladder, bile passages, and portal vein negative.

Pancreas firm, light brown in color. Near the head there is a small reddish body, size of a pea. Several large Pacinian corpuscles near pancreas.

Mesentery poor in fat. Glands greatly enlarged, not pigmented. On section, many are reddish or pink.

Retroperitoneal glands enlarged; the hemolymph glands much enlarged, and of a chocolate-brown color.

Genitals small, otherwise negative. Tissues about rectum thickened and infiltrated. Rectal fistula opening through perineum near anus, filled with gauze; purulent discharge. No tubercle bacilli in pus.

Red marrow hyperplastic; no changes in fatty marrow of long bones of lower extremities. Peripheral lymph glands not enlarged. Negative.

Microscopic. Heart. Brown atrophy and fatty degeneration. *Lungs.* Atrophy, edema, healed tubercles. *Spleen.* Marked atrophy, no hemosiderosis. *Kidneys.* Atrophy, connective-tissue increase, slight hemosiderosis, convoluted tubules, small hyaline scars (tubercles?). *Stomach.* Chronic gastritis with hyperplasia, healing ulcers. *Intestines.* Chronic enteritis. *Liver.* Atrophy, hemosiderosis of peripheral zone of lobules, small degeneration cysts (?). *Pancreas.* Fatty infiltration, slight hemosiderosis. *Bone-marrow.* Megaloblastic, no lymphoid areas in fatty marrow.

Hemolymph Glands. See below.

Pathologic Diagnosis. Pernicious anemia; chronic enteritis; healing gastric ulcers; rectal fistula; hemosiderosis of liver, kidneys, etc. General atrophy, fatty degeneration of heart.

CASE VII.[1]—Mr. J. L., German, aged sixty-one years, farmer by occupation, was admitted to Medical Clinic December 5, 1901. Patient came to

[1] This and the following case have been added to the article since the Washington meeting.

hospital because of "gas on stomach," vomiting at times, heavy pain in stomach after eating, loss of weight and strength. Family history negative. Had good health up to the age of fifty years. At that time had a severe attack of "dysentery," lasting several weeks. After this his stomach began to trouble him, pain and shortness of breath, until relieved by eructations of gas. Starchy foods gave most trouble. Had a sour vomitus, which "bit" his mouth. This condition lasted until one year ago, when he began to lose appetite and strength. At times when he is feeling worse his skin becomes quite yellow. Mind has been much disturbed, has had persecution delusions, and at one time attempted to murder his family. Has had lumbago and slight attacks of "rheumatism." Bowels regular for the greater part of the time, but has attacks of diarrhea, lasting several days.

Physical Examination. Patient looks very ill, markedly cachectic, expression weary and drawn, active dorsal position. Height, five feet nine inches. Present weight, 114 pounds; ten years ago weighed 156 pounds; one year ago 130 pounds. Limps in walking; has a slight lateral curvature, causing prominence of left side and scapula. Musculature small and flabby; panniculus absent. Skin loose, inelastic, dry, extremely sallow, with yellow tint; scleræ white. Mucous membranes rather pale; tongue small, smooth, without coat; papillæ very short. Teeth rotten; only a few snags in mouth. Slight soreness of gums. No edema at ankles. Examination of joints negative. Jugulars very prominent.

Lung boundaries sixth rib on right, sixth intercostal space on left. Hyperresonance all over. Auscultation negative.

Percussion of heart negative. Low-pitched, rather harsh systolic murmur at apex, scarcely heard in left axilla. Second sound at apex not made out. Pulmonary second not accentuated; aortic second negative. Radial artery shows a diffuse hardening; pulse from 52 to 54, regular, moderately strong.

Edge of ribs touch iliac crests. Thorax appears pressed in at sides Double inguinal hernia, most marked on left. Abdomen below level of ribs slightly fuller below umbilicus. Pubes very prominent. Abdominal walls very thin and lax. Liver dulness extends to margin of ribs; liver not distinctly palpable. Splenic dulness not enlarged; organ not palpable. Distention of stomach not satisfactory. Digital examination of rectus showed internal piles; prostate not enlarged.

Blood Examination, November 9th. Red cells, 1,626,400; leukocytes, 4838; hemoglobin, 40 per cent. Differential count of 242 cells: Lymphocytes, 14.5 per cent.; mononuclear, 8.4 per cent.; polynuclear, 54 per cent.; eosinophile, 1 per cent.; degenerating, 22 per cent.; megaloblasts, 0.5 per cent.

Poikilocytosis very marked; many megalocytes, about 33⅓ per cent.

Examination of stomach washing after test-meal showed moderate amount of mucus, small amount of pus, no free or combined HCl, no starch digestion, positive lactic-acid test. Urine contained numerous cylindroids and few hyaline casts.

Patient's condition remained about the same for some time. On February 27, 1902, he was referred to Surgical Clinic for operation for piles. On March 10th lower extremities became edematous. The last blood examination, made on March 25th, showed marked improvement; both hemoglobin and number of red cells increased. After this time he began to fail rapidly. Cystitis followed the operation for hemorrhoids. Condition of mind worse; attempts starvation. Discharged April 24th. After leaving hospital grew worse very rapidly. Complete loss of mental powers. Skin very yellow at times, with small scattered hemorrhages over trunk and abdomen. Died May 17, 1902.

Autopsy at patient's home by Dr. Warthin, May 18th.

Autopsy Protocol. Body of medium build; slight posterior and lateral curvatures; lower edge of ribs touches iliac crests; left side very prominent. Musculature very small; great emaciation; no panniculus; lower extremities edematous; skin dark, sallow, with decided yellow tinge, dry and rough; numerous punctiform hemorrhages over trunk and thighs; pigmented patches over face and arms; teeth absent; gums ulcerated; rigor mortis present throughout; abdomen scaphoid, much below level of ribs. On section muscles are deep brown in color and very dry. Fat tissues deep orange-yellow.

Heart small, very soft and flabby. Few small punctiform hemorrhages in pericardium. Large tendinous spots on anterior and posterior surfaces. Subepicardial fat greatly increased, light orange-yellow, near the apex showing serous atrophy. Large antemortem clots in auricles. Heart muscle pale yellowish, very soft and easily torn. Right ventricle dilated. Slight calcification and thickening of aortic flaps. Large patch of calcification in endocardium of left ventricle. Otherwise heart is negative.

Lungs very voluminous; no fluid in cavities; few small adhesions. On section very pale, slight anthracosis, much edema. Areas of bronchopneumonia in right lower lobe. Bronchial glands negative.

No fluid in peritoneal cavity; large intestine moderately distended; stomach and small intestines collapsed; stomach lying almost vertically, the pylorus below level of umbilicus; spleen large, extending below edge of ribs; liver about a hand's breadth above the edge of ribs in right nipple line; omentum poor in fat of a deep orange-yellow.

Spleen about four times normal size; capsule stretched, smooth. On section deep red in color, very soft. Trabeculæ and follicles covered up by pulp.

Adrenals slightly atrophic, otherwise negative.

Both kidneys smaller than normal; fatty capsule well developed; fibrous capsules adherent; cortical surfaces rough and irregular. In both kidneys numerous soft yellowish elevations scattered over cortical surface. Around some of these there is a reddish zone. On section both kidneys show abscesses of varying size, extending from pelvis to cortex, forming the yellowish elevations seen on the latter. Kidney substance between the abscesses is pale yellow, cloudy, and softened, containing numerous hemorrhagic areas.

Pelvis dilated, mucosa thickened and covered with purulent exudate. In the exudate are numerous small gritty particles. Both ureters dilated, the mucosa thickened. Bladder wall greatly thickened; in the mucosa are numerous ulcers of varying size having undermined edges and filled with pus and phosphatic sand. Prostate small; genitals negative.

Mucosa of small intestine atrophic, very anemic. Large intestine filled with soft pale-yellow feces; mucosa very pale; internal hemorrhoids; slight double inguinal hernia, folds of the small intestine resting loosely in capacious shallow sacs without adhesions.

Stomach very small; contains about 250 c.c. of thick mucus, with food remains. The shape of the organ resembles that of a long-handled gourd, the atrophic pyloric end forming the handle, the body being formed by the fundus and cardiac end. The diameter of pyloric half of stomach is less than that of the duodenum. The pylorus is free, admits thumb. Mucosa of pyloric portion atrophic; no appearance of new-growth. Wall of pyloric portion thicker than that of fundus. Mucosa of entire stomach covered with thick grayish mucus.

Pancreas small, lobules atrophic, slight fatty infiltration.

Liver smaller than normal, rather round; left lobe atrophic; capsule slightly thickened over lower edge. On section presents a nutmeg appearance, the general color being a deep reddish-brown. Bile ducts patent; gall bladder small, filled with dark-brownish bile.

Mesenteric glands somewhat more prominent than normally. On section present no unusual appearance. Cervical, axillary, mediastinal, inguinal, and cubital glands not enlarged, apparently normal. At the brim of the pelvis, and extending upward along the aorta and vena cava, are about twenty enlarged and dark-red glands resembling hemolymph glands. The largest forms a cord 5 cm. long and 0.5 cm. in diameter. On section these contain blood sinuses filled with blood. The other lymph glands in this region are pale or brownish, small, and on section appear atrophic. There is no hypostasis or hemorrhage in the neighborhood of these red glands, and they are found side by side with pale glands. Around the renal vessels several similar deep-red glands the size of coffee beans are found. In many of the prevertebral lymphatics a pale-red fluid is present; lymphatics greatly dilated.

The fatty marrow of the long bones of the lower extremities is deep red throughout, being apparently replaced by lymphoid marrow.

The brain and spinal cord were not examined. (No permission. Owing to circumstances no weights or measurements could be taken.)

Microscopic. Heart. Atrophy and fatty degeneration. *Lungs.* Acute and chronic congestion, edema, areas of bronchopneumonia. *Spleen.* Atrophy, acute and chronic congestion, hyaline vessels, increase of reticulum of pulp, great decrease of lymphocytes in pulp, the majority of cells in the pulp are large mononuclear cells, of varying size and shape. Many of these contain pigment, very little of which gives the iron reaction. They also contain red

blood cells in different stages of disintegration. Larger cells containing from two to three nuclei are also numerous in the reticulum and sinuses. A few large giant cells resembling those of the bone-marrow also found. Many of the larger mononuclear phagocytes are colored brown or yellowish; in others the pigment is granular. Small collections of granular pigment of brown color are found throughout the pulp. Only a small portion gives the iron reaction. *Adrenals.* Negative, postmortem change. *Kidneys.* Cloudy swelling, atrophy, acute ascending pyelonephritis. Very little hemosiderosis of convoluted tubules. *Bladder.* Chronic purulent cystitis. *Stomach.* Chronic atrophic gastritis. *Intestine.* Simple atrophy. *Pancreas.* Atrophy, slight increase of interstitial connective tissue. Moderate sclerosis of vessels. *Liver.* Marked chronic congestion (nutmeg liver), lobules atrophic, marked hemosiderosis of peripheral portions of lobules. In the cells of the central portion both hematoidin and hemosiderin are present: many endothelial cells containing the latter are found. *Bone-marrow.* Areas of lymphoid marrow in fatty degeneration; contain few nucleated red cells and few giant cells.

Lymph Glands. Atrophic; follicles of many glands contain hyaline masses; eosinophiles not increased. In the sinuses of many glands numerous red cells are found, also phagocytes containing red cells.

Hemolymph Nodes. See below.

Pathologic Diagnosis. Pernicious anemia, hemosiderosis of liver, chronic cystitis, ascending pyelonephritis, chronic atrophic gastritis, general atrophy and passive congestion, fatty degeneration of heart, lymphoid marrow.

CASE VIII.—Miss Mary McK., aged twenty-seven years, American, was admitted to medical clinic June 7, 1902, complaining of "general weakness." Family history negative. Healthy as a child. Had measles and whooping-cough. Three years ago had "malarial fever" while in Michigan. Was ill with fever for about two or three weeks; no chills. Never well since the attack. During the fever had pronounced epistaxis; this would occur without apparent cause. Has always had tendency to nose-bleeding. Periods established at age of twelve or thirteen years, regular, no unusual flow. Continued regular up to a year ago, when they stopped entirely. Present trouble began three years ago. Easily fatigued. At same time she noticed that she was becoming pale. Appetite variable; sometimes has sharp pain in stomach after eating, frequent nausea and vomiting. Vomitus always yellow from bile, never dark. Is troubled with shortness of breath. Feet swell when she walks; last summer they were swollen all the time, the swelling extending as far as the knees. Often feels dizzy when walking. Has usually two or three loose stools daily. Since last spring has had hemorrhoids, which bleed occasionally, but not profusely. Has frequent attacks of nose-bleed without apparent cause. Complains of blurring and "specks" before the eyes. Is better in winter.

Physical Examination. Patient looks very sick; extremely pale and sallow; very weak. Mind clear, but answers questions slowly. Voice weak.

Mucous membranes very pale. Scleræ white, with yellowish tint from layer of fat beneath conjunctiva. Teeth fairly good, several extracted. Height, five feet six inches; weight, 105 (best weight 140 pounds).

Auscultation and percussion of lungs negative. Broad area of pulsation over precordium. Pulsation very rapid. Apex-beat best felt in fourth intercostal space in nipple line. Distinct pulsation in third intercostal space extending to nipple. Distinct systolic thrill over the greater part of precordium. Dulness begins on third rib, extends to within 1 cm. of nipple, and extends a slight distance to right of sternum in fourth intercostal space. Loud, rather harsh systolic murmur at apex, followed by soft, distinct, diastolic murmur, heard best inside and above nipple and well transmitted to left axilla. In the fifth intercostal space, to the left of the sternum, there are loud blowing systolic and diastolic murmurs, same in the left second interspace, much weaker in the right second interspace, but very loud in middle of sternum opposite third intercostal space. Pulse 124, small, low tension, artery not thickened.

Abdomen slightly below level of ribs, shows a prominence, shape of stomach, just below navel. Succussion sounds in this region. Right kidney distinctly palpable, left not satisfactorily felt. Liver dulness very broad, extending from fifth rib to margin of ribs. Thin edge of liver can be felt. Splenic dulness greatly enlarged, extending from seventh intercostal space to margin of ribs and forward into Traube's space, combining with heart dulness to make this space completely dull. Spleen not satisfactorily felt.

Blood Examination. Red blood cells, 704,000; leukocytes, 2037; hemoglobin, from 13 to 15 per cent. (June 11, 1902). On the 20th the red cells were 546,000; hemoglobin, 14 per cent. Poikilocytosis and endoglobular degeneration marked. Numerous normoblasts and megaloblasts.

Urine contained trace of albumin; no casts.

Patient rapidly grew worse, irregular fever reaching 102° at times, vomiting, hemorrhage from bowel, etc. Died June 25th, at 6.20 A.M.

Autopsy by Dr. Warthin at 7 P.M. of same day.

Autopsy Protocol. Body slender, 157 cm. long. Thorax long and narrow below, right side anteriorly more prominent than the left. Abdomen above the level of the ribs, the distention greatest just below the umbilicus. Musculature small, much emaciated. On section muscles are pale and moist, do not tear easily. Fair amount of panniculus. On section light golden-yellow, slightly moist. Traces of edema over ankles. Rigor mortis is present throughout. Trunk is slightly warm. Skin is very pale sallow, with slight yellowish tint. Very pale hypostasis over back. A number of bluish areas (angiectatic veins) about both ankles. Numerous small pigmented lymphangiomata over the radial side of both forearms. No punctate hemorrhages found anywhere in the skin. Mucous membrane very pale. Teeth in good condition, upper molars absent. Slight layer of yellowish fat over sclerotics.

Brain and spinal cord not examined. No permission.

Diaphragm at level of fourth interspace on both right and left. Mammæ negative. Apex in left nipple line, fourth interspace. Heart extends slight

distance beyond right sternal line. Mediastinal fat in fair amount, light yellow color. No remains of thymus. Pericardial sac lax; contains about 30 c.c. of clear fluid. Heart weighs 332 grams, larger than cadaver's right fist. Both ventricles dilated. Small tendinous spot on anterior wall of right ventricles; otherwise pericardial surfaces are normal. Subepicardial fat greatly increased, completely covering the right ventricle with a thick layer. No hemorrhages beneath the pericardium. Heart contains pale, watery blood, and a very thin layer of whitish clot covering the endocardium of the right ventricle and auricle. Wall of left ventricle measures from 8 to 12 mm. Ventricular cavity greatly dilated, the muscle trabeculæ flattened. Muscle is very pale yellowish-brown, cloudy cooked appearance; is very soft and easily crushed. The columnæ carneæ show moderate degree of "tiger heart." Right ventricle greatly dilated. Wall measures from 6 to 8 mm., from 3 to 5 mm. being of fat. The mitral orifice admits three fingers; valves normal. Aortic admits thumb; semilunar valves negative. Tricuspid greatly dilated; admits entire hand; flaps negative. Pulmonary orifice and valves negative.

Slight amount of clear fluid in both pleural cavities. Left lung weighs 54.5 grams. Pleura entirely free, clear, moist, shining. Lung moderately voluminous. Upper lobe very pale, moderate hypostasis in lower. On section parenchyma yields an abundant fluid exudate on slight pressure. Slight anthracosis. No airless areas. Two small pigmented healed tubercles beneath pleura. Right lung weighs 52.8 grams. Few old adhesions in pleura. On section similar to left lung. Pulmonary vessels negative. The bronchi are filled with foamy fluid; mucosa very pale. Bronchial glands moderately anthracosed. Esophagus and thoracic vessels negative. Cervical glands negative. Mouth and throat not examined. Thyroid small.

No fluid in peritoneal cavity. Peritoneum moist, negative. Omentum rich in fat of a light-yellow color. No subperitoneal hemorrhages. A number of small pale-pink lymph glands in omentum near greater curvature of stomach. Position of abdominal organs negative.

Spleen weighs 336 grams and measures 15 by 9.5 by 4 cm. Enlarged capsule stretched, shows a number of patches of hyaline thickening over anterior surface. No notches in either anterior or posterior edges. Shallow furrow on anterior surface near upper fourth. Consistency very firm; does not flatten. On section very anemic; pulp bluish-red, swollen, and granular, covering up follicles. Pale-pink infarct near upper pole, extending into organ in wedge shape. Consistency of infarct firmer than of surrounding pulp.

Adrenals negative. Slight postmortem change in medullary portions. Left kidney weighs 19.2 grams, normal size and shape. Right kidney weighs 17.6 grams. Both kidneys present the same appearances. Fatty capsules very rich in pale-yellow fat. Fibrous capsules strip easily. Venæ stellatæ not shown. Consistence of kidneys very firm; color pale pinkish-brown; very anemic. Outlines of kidney structures not well marked. Surface very

glistening, semitranslucent, suggesting amyloid. Ureters and bladder negative.

Stomach rather large, dilated, contains about 200 c.c. of sour-smelling food-remains. Wall very thin. Mucosa white, smooth, and very thin. Advanced postmortem digestion. Duodenum contains yellowish fluid, with food-remains, sour odor. Mucosa very pale, thickened between the atrophic folds. Appearance resembles the "état mammeloné." Ileum distended; contains very pale, soft, fecal material. Mucosa atrophic, very pale. No enlargement of Peyer's patches or solitary follicles. No hemorrhages; no parasites. Appendix 10 cm. long, very slender, narrow lumen containing light-colored fecal material. Has large mesentery. Cecum distended. Colon above sigmoid distended, containing gas and soft light-colored feces. No blood, no evidences of hemorrhage. Mucosa pale brown. Sigmoid contracted, empty. Upper portion of rectum contains pale, putty-like feces. No signs of blood. Mucosa of lower portion of rectum injected. Just above anus there is a ring of flattened hemorrhoids completely encircling bowel. From these there is evidence of hemorrhage in the shape of fresh blood and small clots. On section tissue of submucosa about hemorrhoids is infiltrated with blood. Hemorrhage is apparently by diapedesis. Mucosa of anus is contracted, covered with whitish coating as if free from the action of some caustic.

Liver is enlarged, weighing 2624 grams; breadth, 27 cm. Right lobe measures 23 by 19 by 5 cm; left lobe 11 by 8 by 4 cm. Rather flattened, the sagittal diameters increased. Slight thickening of capsule along lower edge (slight corset liver). Anomalous furrow in the upper part of left lobe. On section very anemic; central veins show only in peripheral portions; here they are much dilated, giving a marked nutmeg appearance. Cut surface is pale yellowish-brown, the central zones of the majority of lobules being a lighter yellow. Peripheral portion browner. Slight fatty smear. Surface shows fatty shine. Gall-bladder is very small, not dilated; contains very thick brownish bile, with small amount of coarse dark sand composed of pigment, largest size of mustard seed. Bile passages patent. Pancreas very pale; shows beginning postmortem change. Portal vein negative.

External genitals negative. Uterus 3.5 cm. long; breadth of fungus, 8 cm.; of cervix, 1.5 cm. Endometrium negative. Vagina very small; rugæ marked. Hymen apparently intact. Ovaries of normal size; ripe follicle on surface of left.

Peripheral lymph glands small and pale. Mesenteric glands not enlarged, very pale. No enlargement of prevertebral glands, the lymph glands small and very pale, the hemolymph glands not hyperplastic, and distinguished from the former only by their uniform pale-pink color. Small amount of pale-red fluid in the lymphatics.

Body contains very little blood.

Fatty marrow of long bones completely converted into deep-red lymphoid marrow.

Microscopic. Lungs. Atrophy, acute congestion, and edema. *Heart.* Fatty degeneration, infiltration, and cloudy swelling. *Spleen.* Marked congestion, atrophy of lymphoid tissue of pulp, hyperplasia of reticulum; blood spaces in many places appear gland-like, lined by hypertrophic endothelium. Many cells along the walls of the sinuses show phagocytic action, containing red cells in various stages of disintegration and a diffuse yellow pigment, which does not give the iron reaction. No trace of iron reaction in spleen. Follicles very atrophic, widely separated. *Adrenals.* Negative. *Kidneys.* Simple atrophy; great increase of interstitial connective tissue. Cells of convoluted tubules filled with coarse granules of yellowish-brown pigment giving the iron reaction. Greater amount of hemosiderin in kidney than in liver. Small nodules of calcification in connective tissue. No amyloid. *Liver.* Lobules atrophic. Marked fatty degeneration of liver cells in central portion of lobule. Very little pigment in degenerated cells, the hemosiderin in central portion of the lobules being almost entirely in endothelial cells. Moderate hemosiderosis of liver cells of peripheral portion. In some areas the capillaries of central zone greatly dilated. A few small collections of leukocytes in Glisson's capsule. *Stomach.* Atrophic; shows complete postmortem necrosis of mucosa. *Duodenum.* Chronic hyperplastic duodenitis. *Pancreas.* Postmortem change. *Lymph Glands.* Atrophic; large masses of hyalin in the follicles of many of the glands. Bloodvessels dilated. Lymph sinuses dilated, containing many red blood cells, also phagocytes containing disintegrating red cells. *Hemolymph Glands.* See below. *Bone-marrow.* Fatty marrow completely replaced by lymphoid marrow, containing few nucleated red cells and few giant cells.

Pathologic Diagnosis. Pernicious anemia, hemosiderosis of liver and kidneys, fatty degeneration and dilatation of heart, chronic duodenitis, general atrophy, lymphoid transformation of fatty marrow.

General Summary of Cases.

Clinical. The clinical features presented by these eight cases are very similar—progressive weakness and paleness, shortness of breath, gastric disturbances, diarrhea, slight, irregular fever, tendency to hemorrhages, low red blood cell-count, relatively high hemoglobin, presence of nucleated red cells, low leucocyte count, etc.

Pathologic. In all eight cases no direct cause for the anemia was found; the general pathologic conditions were the same: hemosiderosis of liver and kidneys, fatty degeneration and infiltration of the heart, general atrophy, passive congestion and edema, punctiform hemorrhages, etc. In two cases no changes in the stomach were found; in four, chronic atrophic gastritis was present; in one case chronic hyperplastic gastritis, and in one case simple atrophy of this

organ. In three cases the fatty marrow showed no lymphoid change. In two cases small points of lymphoid transformation occurred throughout the fatty marrow, while in three cases the fatty marrow of the long bones was completely changed into lymphoid marrow.

The diagnosis of pernicious anemia may be safely based upon the above characteristics in all of the cases, with the possible exception of Case III. Both the clinical symptoms and the pathologic findings make this case unique. The marked tendency to hemorrhage, the active hemolysis in the circulating blood, as shown by the blood examinations, the sarcoma-like hyperplasia of the retroperitoneal lymph glands, make the diagnosis doubtful, and both Dr. Dock and myself have hesitated in classifying this case under any definite head. Since the hyperplastic changes in the retroperitoneal lymph glands appear to take their origin from the hemolymph glands I have included this case in this group, although the diagnosis of early stage of leukemia, lymphosarcoma, or hemolytic poison must also be considered.

LYMPH GLANDS. GROSS APPEARANCE.

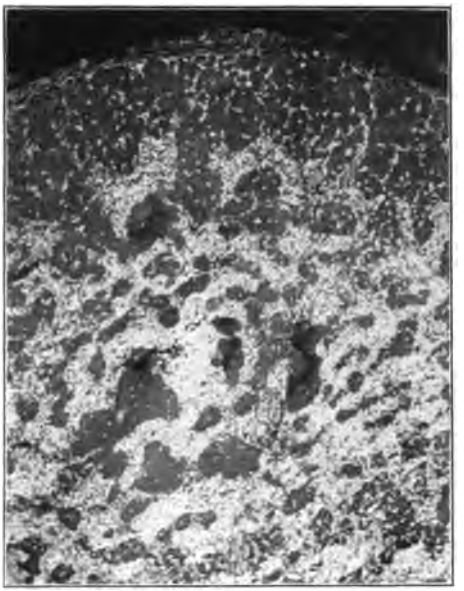
Case.	Peripheral.	Mesenteric.	Prevertebral.	Hemolymph.
1	Slightly enlarged, more or less brown pigmented.	Slightly enlarged, pale pink.	Enlarged, brownish-red.	Enlarged, brownish-red.
2	Not enlarged; negative.	Not enlarged; negative.	Not enlarged, pinkish or brownish.	Not increased in number, not enlarged; pink or brownish; three in omentum pink.
3	Not enlarged; negative.	Not enlarged; negative.	Greatly enlarged, red.	Enormously enlarged lymphosarcoma (?); red.
4	Negative.	Moderately enlarged, pale, homogeneous.	Greatly enlarged, brown color.	Enlarged, brownish.
5	Not enlarged; negative.	Not enlarged; negative.	Majority appeared to be hemolymph glands, red or bluish-red, largest, size of bean.	Apparently greatly increased in number, red to bluish-red; not enlarged; size of mustard seed to pea.
6	Not enlarged; negative.	Enlarged, reddish or pink; not pigmented.	Enlarged, brownish.	Enlarged, chocolate-brown.
7	Not enlarged; normal.	Prominent; otherwise negative.	Atrophic, pale or brownish.	Enlarged, deep-red color; sinuses greatly dilated with blood.
8	Small and pale.	Not enlarged; very pale.	Small and pale.	Not enlarged, pale pink; sinuses distended with pale blood.

LYMPH GLANDS. MICROSCOPIC.

Case.	Peripheral.	Mesenteric.	Prevertebral.	Hemolymph.
1	Deposit of hemosiderin.	Congested; in many red cells and pigmented; phagocytes in the lymph sinuses.	Moderate hyperplasia; hemosiderin deposit; many congested; contain red blood cells in lymph sinuses.	Hyperplastic sinuses dilated; increased hemolysis; hemosiderosis.
2	Negative.	Negative.	No hyperplasia; hemosiderin deposit in some.	No hyperplasia; only slight increase of hemolysis.
3	Negative.	Negative.	Extreme hyperplasia resembling sarcoma, but containing lymph sinuses filled with red blood cells.	Tumor-mass of the nature of hyperplastic hemolymph glands or hemolymph sarcoma; marked hemolysis; little hemosiderin; increase of eosinophiles.
4	Negative.	Negative.	Sinuses of majority contain phagocytes filled with pigments.	Sinuses filled with phagocytes containing red cells and pigment; increase of eosinophiles.
5	Negative.	Negative.	Apparently all hemolymph glands; sinuses filled with blood and phagocytes.	Sinuses filled with phagocytes containing red cells and pigment; increase of eosinophiles.
6	Negative.	Lymph sinuses contain many phagocytes, disintegrating red cells and pigment.	Majority apparently hemolymph glands; sinuses filled with blood and phagocytes.	Sinuses filled with pigment containing phagocytes; much hemosiderin; increase of eosinophiles.
7	Negative.	Negative.	Atrophic hyaline masses in follicles; red cells, and phagocytes in sinuses.	Atrophy of lymphoid tissue; sinuses dilated; many phagocytes; small amount of pigment.
8	Negative.	Negative.	Atrophic lymph sinuses dilated; contain red cells and phagocytes.	Atrophic; increased hemolysis; many phagocytes containing red cells, but little pigment; hyaline deposits; sinuses dilated.

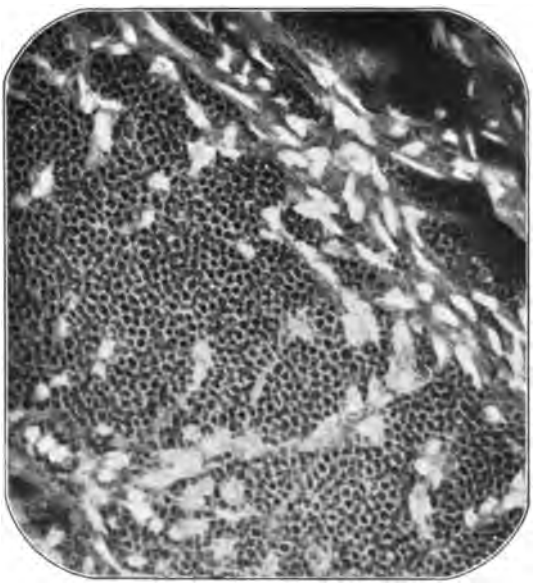
It will be seen from the above that the changes in both lymph and hemolymph nodes vary greatly in degree. In one case only did the peripheral glands (axillary, superficial cervical, inguinal, and cubital) show any change that could be regarded as belonging essentially to pernicious anemia. Likewise the changes in the mesenteric glands were not constant, occurring in but two cases; but in all eight cases changes were found in the prevertebral retroperitoneal lymph and hemolymph glands, indicating a degree of hemolysis greater than that found either in normal conditions or in such diseases as chronic tuberculosis, typhoid fever, sepsis, etc., in which evidences of increased destruction of red cells are also found in these glands. These changes

FIG. 1.



Hemolymph gland, showing dilated blood sinuses; dark areas = blood in sinuses; light areas = lymphoid tissue. × 150.

FIG. 2.



Higher power view of blood sinus from same gland as in Fig. 1, showing the sinus filled with red blood cells, and the delicate reticulum traversing the sinuses. × 750.

may be summed up as follows: Apparent increase in number, or hyperplasia of resting hemolymph glands, dilatation of the lymph sinuses with increase of phagocytes containing disintegrating red cells and pigment; in the lymph glands, dilatation of the lymph sinuses, presence of an increased number of red cells in the latter, increased number of phagocytes, and congestion.

These changes differ so greatly in degree in the different cases as to suggest intermittent rather than continuous hemolysis. In Case II. the evidences of hemolysis were not much greater than normal. In Cases VII. and VIII. there was a great increase in the number of phagocytes containing red cells, but little pigment. In Cases III., IV., V., and VI. the sinuses were filled with pigment-containing phagocytes giving but little iron reaction, while in Case I. the glands were filled with granular hemosiderin, both free and in phagocytes. It seems reasonable to explain these various findings by the theory of intermittent or cyclical hemolysis, death in the different cases occurring at different stages of blood-destruction. This theory is borne out by the clinical history of exacerbations in the symptoms of anemia, intoxication, etc. In three cases (I., V., and VI.) showing a more malignant and rapid termination, the patient dying during an exacerbation, the evidences of hemolysis in the glands were more marked. In the cases dying of progressive weakness, cardiac dilatation, etc., without special exacerbation, the findings are those of less active hemolysis. (Cases II., VII., and VIII.) There is also good reason to believe that in some cases the spleen is the most active seat of hemolysis; in others, the hemolymph glands. This is based upon the fact that in some cases very little hemosiderin, or few phagocytes containing red cells are found in the spleen, while they are abundant in the hemolymph glands. Either the poison causing pernicious anemia acts differently at different times upon the hemolytic organs or more than one hemolytic poison may lead to the disease by stimulation of either splenic, lymphatic, hemolymphatic, or bone-marrow hemolysis. At present nothing can be regarded as proved regarding these points, inasmuch as we know nothing at all concerning the nature of the hemolytic poison of this disease.

The human hemolymph glands may be divided into three groups with reference to the relationship between the lymph and blood systems:

1. Glands with blood-sinuses only.

2. Glands with blood sinuses communicating directly with lymph sinuses.

3. Glands with very slight capillary connection between blood and lymph sinuses.

The second and third varieties are of most common occurrence in man, the first variety in the sheep, goat, and ox. Under normal conditions the amount of blood passing directly into the lymph is probably very small, and the majority of red cells are destroyed by the phagocytes in the lymph sinuses. A certain number of red cells escape these, so that the lymph from these glands always contains a certain number of red cells, this having been interpreted by some observers as proof of the formation of red cells by lymph glands. The majority of mesenteric and retroperitoneal glands belong to the third class.

There is, therefore, always a certain amount of normal hemolysis taking place in these glands. Under pathologic conditions of congestion and inflammation the number of red cells passing into the lymph sinuses to be destroyed, in part, at least, by the phagocytes, is greatly increased, to such an extent sometimes that the lymph sinuses become filled with blood, and the glands come to resemble the hemolymph glands of the first variety. The increased influx of blood into the sinuses leads always to an increased formation of phagocytes, these arising apparently from the endothelial cells lining the lymph sinuses. The abnormal degree of hemolysis thus produced occurs in the majority of infective processes, particularly in sepsis, typhoid fever, and chronic tuberculosis, and may be produced by certain poisons which cause congestion of the lymph glands. Further, lymphatic glands may become so congested that diapedesis of red cells into the lymph sinuses occurs, the same phenomena of phagocytosis and hemolysis taking place. This is particularly well seen in regional lymphatics in the case of local infections. In infective diseases the specific poison, when absorbed into the general circulation, may stimulate the phagocytes of the spleen and hemolymph glands to increased hemolytic activity, either directly or through injury of the red cells.

THE HEMOLYSIS OF PERNICIOUS ANEMIA DOES NOT DIFFER IN KIND FROM THAT OCCURRING NORMALLY OR IN CERTAIN DISEASED CONDITIONS. THE DIFFERENCE IS ONE OF DEGREE ONLY. It is not the object of this paper to over-emphasize the actual amount of hemolysis

FIG. 3.

Large mononuclear cells containing hemosiderin lying in meshes of the reticulum of the blood sinus. × 1000.

FIG. 4.

Phagocytes containing hemosiderin from blood sinus of hemolymph gland. × 1500.

occurring in the lymphatic and hemolymphatic glands in pernicious anemia. The main object is to call attention to the fact that such hemolysis may occur in this disease to a greatly increased degree in these structures, as well as in the spleen. The conclusion to be gathered is that the hemolytic poison does not confine its effects to the portal area, as claimed by Hunter, but is present in the general circulation. Further, as has been pointed out by Hunter, hemolysis is a cellular process performed by the phagocytes of the spleen, lymph glands, hemolymph glands, and bone-marrow in response to the direct stimulus of the poison or of blood cells injured by the poison.

No evidence of the actual destruction of red cells is found in any organ or tissue except the spleen, lymphatic and hemolymphatic glands, and bone-marrow. The hemosiderin found in the liver and kidneys must exist in the circulating blood in the form of some soluble derivative of hemoglobin, which is set free at the seats of hemolysis. This is taken from the blood by the endothelial cells of the liver and kidney (rarely by those of other organs—pancreas, thyroid, adrenals, lymph glands, etc.), transferred to the epithelial cells of these organs, thence to be excreted through the bile and urine. The occurrence of hemosiderosis of the liver and kidneys in pernicious anemia is, therefore, a secondary process only, and is characteristic of pernicious anemia only in so far as the degree of the hemosiderosis is concerned. That the hemosiderin is taken from the blood by the endothelial cells is well shown in Case VIII., in which in the majority of liver lobules the liver cells of the central portion of the lobules having disappeared as a result of chronic passive congestion, the pigment is found in the endothelium. Further, in animal experiments with toluylendiamin the hemosiderin appeared first in the endothelium of the liver capillaries and later in the liver cells.

In some of the cases there was an apparent increase of hemolymph glands. At present it cannot be stated whether this is due to an actual new formation or to a hyperplasia of minute resting glands. It is more probable that the latter explanation is the correct one, the glands becoming more prominent as a result of their increased functional activity. The change in the lymphatic and hemolymphatic glands, to be regarded as many times, if not always, an important feature of the pathology of pernicious anemia, is: *Increase in the number of lymph glands showing diffuse red color, or spotting or*

streaking with red. That the changes described above occur in every case of pernicious anemia cannot be proved by their occurrence in every one of my eight cases. The fact that changes have been so rarely described might be explained by the rarity of changes in the peripheral and mesenteric glands, the relatively insignificant character of the gross appearance, and the fact that microscopic examination is necessary for the ultimate determination of the nature of the glandular changes. Moreover, it is possible that there is a lymphatic or hemolymphatic form of pernicious anemia as well as a splenic, the changes described above being found only in the former.

Weigert's case, the three cases noted by Osler of deep-red glands resembling spleen tissue, Schumann's case of enlarged and hemorrhagic glands, Müller's case of bright-red glands, the three cases of Eichhorst, I regard as resembling my cases, the red glands to be hemolymph glands or lymph glands showing increased hemolysis. Three of my cases (V., VI., and VII.) were almost exactly like Weigert's in the number of blood-containing glands and the large amount of blood in the lymphatics. *No evidence of red blood cell formation in the lymphatic or hemolymphatic glands was seen in any of the eight cases. The presence of nucleated red cells in the sinuses is explained by their presence in the circulating blood.*

Returning again to Case III., the great hyperplasia of lymphoid tissue containing blood sinuses apparently arising from the hemolymph glands gives this case great pathologic interest. The microscopic appearances suggest a direct conversion of fat tissue into lymphoid, and one is reminded of the new formation of hemolymph glands occurring after splenectomy as described by Tizzoni, Winogradow, Mosler, and myself. The term "hemorrhagic telangiectatic lymphoma," as applied by Mosler to such new formations, could be used in this instance with propriety.

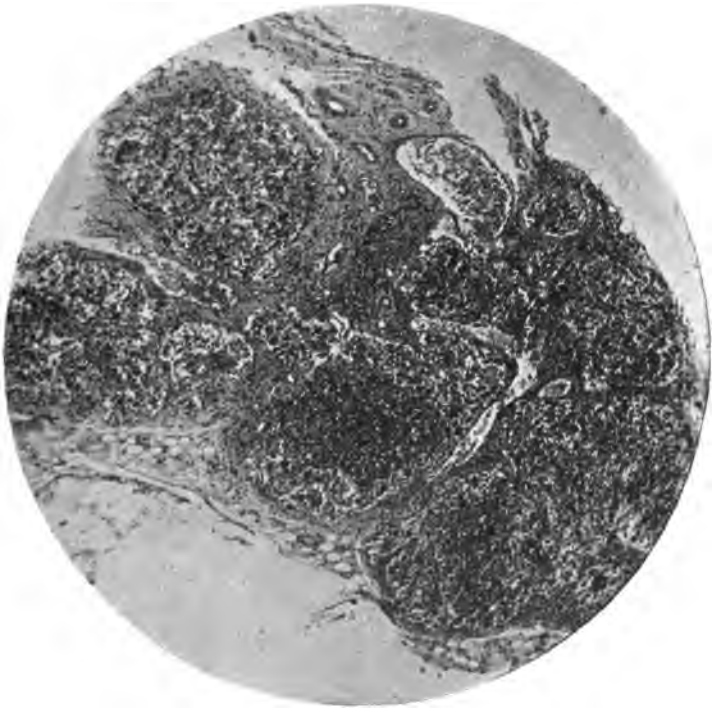
An increase of eosinophiles in the hemolymph glands was noted in four of my cases—in three associated with the presence of much pigment, in one case with little pigment.

EXPERIMENTAL. Hunter having shown that toluylendiamin caused hemolytic action of the spleen similar to that of pernicious anemia, experiments were undertaken to show the effects of this poison upon the hemolymph and lymphatic glands. The sheep was chosen for this purpose, inasmuch as the hemolymph glands in this animal are

FIG. 5.

Section of tumor-like hyperplasia of retroperitoneal prevertebral glands in Case III. (angiectatic lymphosarcoma or hemolymphosarcoma?). × 100.

FIG. 6.



Cervical hemolymph node from Case V. Peripheral sinuses filled with pigmented phagocytes. × 100.

very large and numerous. In two cases—one of acute and the other of chronic poisoning with toluylendiamin—the hemolymph glands gave evidences of increased hemolysis, as shown by the increased number of pigment and cell-containing phagocytes. Extreme congestion of the lymphatic glands was also produced, leading to diapedesis of red cells and hemolysis in the lymph sinuses. Increase of eosinophile cells was also noted in some of the glands. In a third sheep which had been splenectomized two months previously intense hemolysis was shown by these glands and a hemosiderosis of the liver resembling that of pernicious anemia. The increased hemolysis in this case may be explained by the compensation on the part of the hemolymph glands for the spleen. By these experiments it may be taken as proved that toluylendiamin excites not only the cells of the spleen to phagocytic hemolysis, but also those of the lymph and hemolymphatic glands. The close similarity between the action of toluylendiamin and the poison of pernicious anemia is thus further shown.

CONCLUSIONS. 1. Pernicious anemia is essentially a hemolytic disease, the hemolysis due to some as yet unknown poison comparable in its effects upon the blood and blood organs to the action of toluylendiamin. Whether autointoxication or infection, remains yet to be determined.

2. The poison of pernicious anemia stimulates the phagocytes of the spleen, lymph, and hemolymph glands and bone-marrow to increased hemolysis (cellular hemolysis). Either the phagocytes are directly stimulated to increased destruction of red cells or the latter are so changed by the poison that they themselves stimulate the phagocytes. The hemolysis of pernicious anemia differs only in degree, not in kind, from normal hemolysis, or the pathological increase occurring in sepsis, typhoid, etc.

3. It is not improbable that from the destruction of hemoglobin poisonous products (histon?) may be formed which have also a hemolytic action. A vicious circle of hemolysis may thus be produced. No proof of this exists at present.

4. The hemolysis of pernicious anemia is not confined to the portal area as according to Hunter, but in some cases at least takes place also to a large extent in the prevertebral lymph and hemolymph nodes and bone-marrow. In the majority of cases the spleen is the chief

seat of the blood destruction. No evidences of hemolysis in the liver capillaries were found. The hemosiderin of the liver and kidneys is carried to the organs as some soluble derivative of hemoglobin, is removed from the circulation as hemosiderin by the endothelium, and then transferred to the liver or kidney cells. The deposit of iron in these organs is of the nature of an excretion.

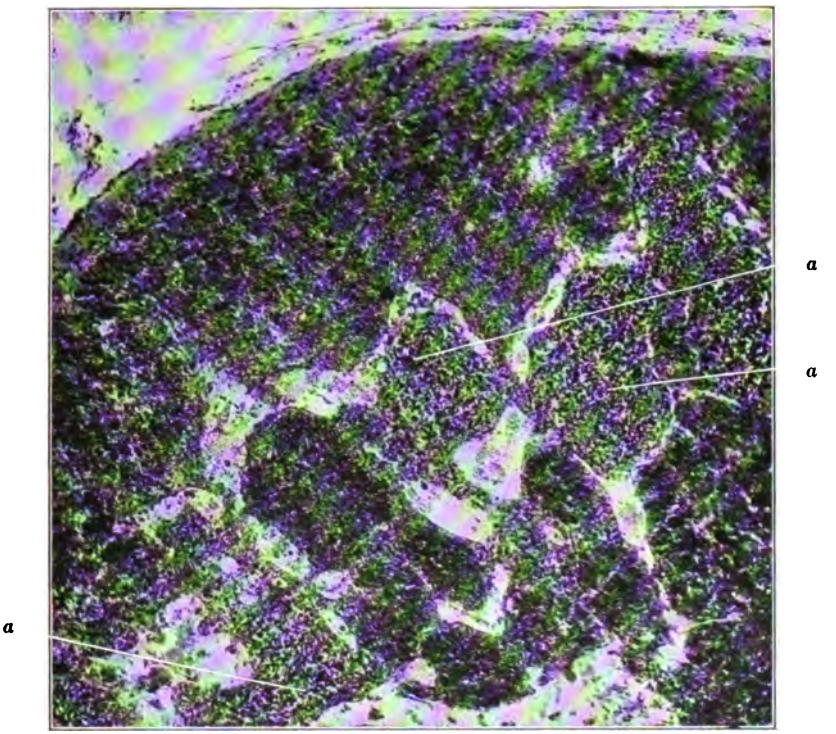
5. In the majority of cases only slight reaction for iron is found at the sites of actual hemolysis—spleen, lymph glands, etc. The greater part of the pigment in the phagocytes of the spleen, lymph glands, and bone-marrow does not give an iron reaction while in a diffuse form. When changed to a granular pigment the iron reaction may usually be obtained. The change to hemosiderin is for the greater part accomplished by the endothelium of liver and kidneys.

6. The varying pathologic conditions found in these different cases of pernicious anemia can be explained only by a theory of cyclical or intermittent process of hemolysis. This theory is also borne up by the exacerbations so frequently seen clinically.

7. The lymphoid and megaloblastic changes in the bone-marrow do not form an essential part of the pathology of pernicious anemia, and are to be regarded as of a compensatory nature, an increased activity of red cell formation to supply the deficiency caused by the excessive hemolysis.

NOTE.—The full bibliography of the references in this paper is omitted because of its great length. My thanks are due to Dr. Bond, of Richmond, Ind., for the photographs of Figs. 1, 2, 3, and 4.

FIG. 7.



Retroperitoneal hemolymph node from Case VII., showing great dilatation of blood sinuses. The dark areas are the blood sinuses filled with red cells and phagocytes; the light spaces are the dilated lymph sinuses containing lymph, but no blood. Example of gland with blood and lymph sinuses entirely separate. *a*, *a*, *a*. Small islands of lymphoid tissue. × 100.

CASE OF CYSTIC DEGENERATION OF BOTH KIDNEYS.

By I. N. DANFORTH, A.M., M.D.,
OF CHICAGO.

On August 23, 1895, I was first consulted at my office by Mr. W——, a hale and hearty-looking man, aged thirty-six years, five feet eight inches in height, weighing 150 pounds, and manifesting every outward sign of vigorous health. He was married and the father of two healthy children. He was manager of a large manufacturing concern, a position involving large responsibility and calling for the exercise of vigorous powers of body and mind. His personal history was quite negative, having had no illness of any account, no bodily injury, no specific infection, no intemperance in the use of alcoholics, although he admitted that he smoked pretty frequently. Two years prior to his first visit to me a little albumin was discovered in his urine, but it disappeared in a short time, and he ceased visiting his physician, as he had no symptoms or discomfort which seemed to require treatment. In the winter of 1894 he had a somewhat severe attack of "la grippe," and was two weeks in bed, but I cannot learn that he had any unusual symptoms, or that any examination of the urine was made at that time. My first examination (August 23, 1895) was made in a very hasty and slovenly manner, as I was very much occupied, and a "snap-shot" diagnosis of interstitial nephritis was made. A few days later I saw him again under more favorable conditions, and arrived at once at the conclusion that the case was one of cystic disease involving both kidneys. He had considerable arterial tension, a somewhat hypertrophic left ventricle, without valvular lesion, and admitted having occasional occipital headache, with momentary attacks of vertigo, and sometimes slight blurring of vision of very brief duration. His digestion seemed unimpaired, and his general appearance

was that of a vigorous, well-nourished, and able-bodied man. I was particularly struck by his quick, decisive manner, his prompt, ready, and intelligent answers, and other evidences of an active brain, unimpaired and unembarassed by toxemia. His urine was pale and clear, slightly acid and with a specific gravity of 1010, and albumin to the amount of one-half gram to the liter, as determined by Esbach's method. There was 1 per cent. of urea, as shown by the hypobromite test, and, as he was passing about 3000 cubic centimeters of urine in the twenty-four hours, it followed that he was excreting about the normal amount of solids. The microscope showed plenty of leukocytes and epithelia, both ovoid and polygonal, but no tube casts. There was no crystalline sediment.

The patient's abdomen was noticeably protuberant, with prominent lateral bulging on either side, and a well-marked sulcus in the median line, and these characteristics were especially noticeable when the patient stood erect. Examination of the abdomen with the patient lying on his back, disclosed the presence of an enormous reniform tumor in each lumbar region, extending above so as to occupy the entire hypochondriac region, and below so as to occupy the entire iliac region. They also occupied the mid-region of the abdomen, so as to actually come in contact with each other when the patient was in the prone position, although they were easily separable and readily outlined by palpation. Nodulations and protuberances could be easily made out, as well as the fact that they were very numerous, and varied greatly as to size. It was easy enough to determine that these protuberances contained a thin, watery fluid, as the fluctuations peculiar to a thin fluid were plainly recognizable. The diagnosis of general cystic degeneration of the kidneys, therefore, seemed warranted, and, of course, the questions of prognosis and treatment were settled as soon as the diagnosis was established.

The history of the case during the three years following my first connection with it is interesting, although uneventful. The urine was always abundant in quantity, rarely less than 2000 cubic centimeters, and frequently more than three thousand in the twenty-four hours ; it was usually clear, limpid, and watery, but now and then it would appear more or less cloudy with mucus ; it was generally odorless, and never offensive; the albumin ranged from a minimum of one-tenth to a maximum of one-half grain to the liter (Esbach) ;

the specific gravity ran from 1004, the lowest, to 1015, the highest point, but these extremes only occurred at intervals, the usual average being about 1010; the urea sometimes fell as low as four-tenths of 1 per cent., and occasionally rose to one and seventy-five hundredths, with a specific gravity of 1015; and on one occasion it reached 2 per cent., with the same specific gravity. It generally ran from five to seven-tenths of 1 per cent. These data would give an average of from forty-five to sixty grains of solids for the twenty-four hours, as calculated by the coefficient of Häser, or about the average for a healthy man. But the urea was nearly always less than the quantity demanded by normal estimates, and this was apparent also from the slight indications of cumulative uremic poisoning already mentioned. The microscopic findings were quite negative; leukocytes and epithelia in varying, but never large numbers; occasionally a few shrivelled red blood globules; and now and then a few crystals of uric acid, sodium urate, or calcium oxalate made up the sum total. Of course, no tube casts were found, although they were, on one occasion, reported to be present before I saw the case.

The conditions—*all* the conditions—which I reported remained practically unchanged during the first three years of my attendance. Occasional attacks of slight illness from colds, indigestion, headache, etc., manifested themselves, but they behaved precisely as they would in a man with two healthy kidneys. The patient attended to a large business all the time, and suffered and surmounted the annoyances caused by strikes, business reverses, bank failure, fires, and all things else incident to a large manufacturing business, with the fortitude of a man of robust mind and body, and his quick motions, elastic step, ruddy complexion, and active mind, gave no hint of the fact that both his kidneys were in a state of anatomic chaos.

Of course, I made frequent examinations of the kidneys, and, in fact, I made some futile attempts at measuring them, for the purpose of determining their rate of growth or enlargement. I soon became satisfied that a very slow process of enlargement was going on, with almost mathematic symmetry, so that the shape or form of the growing tumors preserved a close resemblance to the kidney. The treatment was practically nothing. The bowels were kept free

by the use of salines (usually Hunyadi water), and the attempt was made to keep the patient on a non-nitrogenous diet, but he rebelled and ate about what he pleased. When I first saw him I prescribed potassium citrate. The patient imagined that he was materially aided in excreting urea by this remedy, and so I frequently prescribed it in doses of ten to twenty grains, four times a day; and it is quite true that on several occasions I found a notable increase of urea after he had taken potassium citrate a few days. No other treatment was employed unless temporarily demanded for some temporary ailment which did not directly implicate the kidneys.

Such is the history of the first three years of my connection with this case, and such is practically the history of an unknown number of years before I saw the case.

About six months prior to the patient's death a change took place. The urine lessened in quantity and became turbid; the albumin increased gradually but progressively; slight hematuria appeared occasionally; the urea remained about the same, or generally about half of 1 per cent. At this time the microscope showed a great increase of leukocytes, epithelia, amorphous granular deposit, cholesterin crystals, and now and then blood globules. The patient complained of abdominal distention and weight, and he also had headache, vertigo, and disturbed or uncertain vision. But he resolutely kept about his business in spite of all remonstrance or advice. No increase in the size or feeling of the tumors could be detected by palpation.

On April 6, 1899, he called at my office, for the last time. He had moderate hematuria, increased albuminuria, and was passing only a small quantity of dark, muddy urine; he was sent to his home in a neighboring suburb, and advised to go to bed and call his family physician. On April 10th I was called in consultation. He was now having profuse hematuria, nausea, vomiting, headache, with a temperature of 102° F. April 12th I was again called, and found the symptoms much the same. The urine was scanty, and seemed to consist more of blood than of urine; nausea and vomiting very troublesome; temperature 100° F. to 102° F.; no pain or tenderness in either kidney. April 21st I was again in consultation, and found substantially the same symptoms, which were uninfluenced by treatment. There was at this time considerable

FIG. 1.

Left kidney. Interior. Weight, five and a half pounds.

FIG. 2.

Left kidney. Exterior. Weight, five and a half pounds.

FIG. 3.

Right Kidney. Interior. Weight, six pounds.

FIG. 4.

Right Kidney. Exterior. Weight, six pounds.

mental dulness, tending toward coma. April 21st the patient died, having been comatose for several hours before death. It was only after considerable diplomacy that we were able to get permission to examine and remove the kidneys, but we were forbidden to do any more than that. We were able, however, to determine that the liver, spleen, and pancreas were apparently healthy; at least neither of these organs gave any indications of cystic change to the naked eye. The kidneys were enormously enlarged; the right one weighed six pounds, and the left one five and one-half pounds, several hours after removal from the body and after a considerable quantity of fluid had escaped by leakage. At least ten or twelve ounces should be added to each kidney to represent its true weight during the lifetime of the patient. Both kidneys had undergone perfect and complete cystic degeneration, not a trace of normal tissue being discernible in either organ. I feel pretty confident about this, as a careful examination was made by several of us in the pathologic laboratory of the Northwestern University Woman's Medical School. The cysts varied in size from a small pea to a hen's egg; the walls were thin and translucent; they were generally filled with a clear, watery fluid, which was somewhat cloudy, but a few of the larger cysts contained blood. A microscopic examination of the watery fluid from one of the larger cysts showed a few, small, round cells like leukocytes, a few nucleated pavement epithelial cells, crystals of cholesterin, and some amorphous granular matter, probably derived from broken-down disintegrated cells. The fluid also contained a little urea and a little albumin.

The accompanying photographs give a fairly good idea of the external and internal appearance of these remarkable organs. So far as I have been able to learn, no larger specimens of cystic kidneys have found their way into any pathologic museum in this country.

It is an interesting fact that the patient's sister—still living and in good health—has also cystic disease of the kidneys, as was determined by exploratory operation by the late Dr. Fenger some years ago. The patient's father died at the age of fifty-nine years of some acute attack, said to have been la grippe, in 1892. His mother died at the age of forty years of a "congestive chill," after a very brief and sudden illness. Both parents were in perfect

health, apparently, up to their respective fatal attacks. One sister died at the age of thirty of some gastric disease, which was diagnosed cancer.

One brother is living, perfectly well, at the age of thirty-three years, although I have not been able to verify this statement by a personal examination. One sister has bilateral cystic kidney, but is apparently in perfect health, as I have already stated.

The patient left two sons, now aged thirteen and nineteen years, respectively, and apparently in vigorous health. I have tried to get an opportunity of examining them for the purpose of determining the possible presence of cystic kidney, but cannot induce them to allow me to do so.

There does not seem to be a strongly marked hereditary tendency to polycystic kidney. M. Bar, quoted by Henry Morris[1] "observed the polycystic lesion in the kidneys of three successive children born of the same mother, each of whom presented the cystic degeneration in a different degree." Morris also relates one other case in which two children of a family of six had bilateral cystic kidneys.

I have seen only one other case of polycystic kidney, and this occurred in an unmarried woman, aged forty years, without hereditary antecedents. It was a typical case of bilateral disease. The enlargement was not extensive. The right kidney weighed twenty-three ounces, the left twenty-four and one-half ounces; but the cystic change was complete.

In conclusion I wish to emphasize three points of special interest in the foregoing case:

1. The enormous size of the kidneys. The two organs during the life of the patient weighed more than thirteen pounds, or about twenty-five times the weight of the normal kidneys. Yet these colossal masses did not seem to produce much suffering or inconvenience. The patient frequently told me that he did not realize any inconvenience from weight, pain, or distention. He frequently complained of constipation and a sense of oppression or fulness after eating heartily, but simple aperients were always competent for the relief of the former, and no special treatment was ever required for the latter. So gradually had these giant kidneys

[1] Surgical Diseases of the Kidney, p. 656.

acquired their dimensions that the patient scarcely realized their presence; it was a remarkable and very extreme case of toleration.

2. The perfect, complete, and absolute metamorphosis of the kidneys into a congeries of cysts is also noteworthy. I could not detect in any portion of either kidney, by the naked eye or with an ordinary hand lens, anything which indicated the presence of a particle of true renal parenchyma. It is possible that a prolonged and exhaustive search might have resulted in the discovery of a few minute islets of renal tissue, but I think not, as I feel confident that the examination which I and my associates made was careful and minute enough to determine this point. The process of cystic degeneration was complete. It is, of course, impossible to decide absolutely whether the cystic change was congenital or postnatal; whether it began during the intra-uterine life of the patient, and continued thereafter in uninterrupted progress, or whether it was altogether a postnatal pathologic process. But I venture the conjecture that it began during the intra-uterine life as an arrest or fault of development, and that it continued during life, at least to the extent of a progressive increase in the size of the cysts.

3. Another remarkable fact is the vigorous health and great activity of the patient. He managed a large business, and it required an active brain and a vigorous body. His appearance was that of an unusually healthy man; his step was quick and elastic, and he did not hesitate to run or jump when he found it expedient; he did not engage much in games like bowls or golf, because he found it inconvenient to "stoop over" on account of the presence of his abdominal impediment, but he showed absolutely no lack of muscular development or bodily nutrition. His mental outfit was perfect. He was cheerful, witty, quick at repartee, animated, and ready in conversation, and the peer of any of his competitors in comprehending a business proposition. In fact, when the various branches of the industry in which he was engaged formed a "trust," he was chosen "manager" of the amalgamation.

I have already remarked that he was the father of two healthy children, who give no evidence of any physical or mental defects so far as I can determine without a physical examination, which they decline.

TUBERCULOUS PERICARDITIS:

FOLLOWED BY REMARKS UPON PARACENTESIS AND INCISION.

By BEVERLEY ROBINSON, M.D.,
OF NEW YORK.

Two cases of this somewhat rare disease have been under my care within the past eighteen months. In both cases autopsies were obtained—the one complete, the other only embracing the examination of the heart and pericardium. In one of these instances the pericardium was aspirated several times; in the other it was not considered necessary or judicious to operate. The history of my first case was read at a meeting of the Practitioners' Society,[1] October 11, 1901, and the specimen shown. The case was discussed by the members.

During the past eighteen months I have also taken care of two other cases of pericarditis. Of these, one occurred as a complication of Bright's disease; the other apparently of rheumatic origin. I shall refer to these later in my remarks upon paracentesis.

In certain instances of tuberculous pericarditis it has been noted that there was no evidence of tuberculous deposit in the adhesions which were present. In those instances more numerous, where tubercles are discovered in the adhesions, they may appear like grayish areas at the line of union of the parietal with the visceral layer. In 1048 autopsies, Wells[2] found tuberculous pericarditis 10 times, which formed about 8 per cent. of all cases of pericarditis recorded by him. It is not limited to adults, but may occur quite frequently in childhood or infancy. It is more frequent among men than women. Baginsky reports 15 cases in 4500 autopsies, and of these 4 were purulent. In Osler's autopsies, 1000 in all, there were 7 instances of tuberculous pericarditis.[3]

[1] Medical Record, November 23, 1901, p. 831.
[2] Journal of the American Medical Association, May 25, 1901.
[3] American Journal of the Medical Sciences, 1893, p. 20.

Welch, in his report from Johns Hopkins Hospital, states he has seen 6 cases. Although often spoken of as frequent, it is not shown by references in *Index Catalogue, Transactions of the Pathological Society of London*, etc. Up to 1893 Osler had seen only 17 cases, and yet he writes tuberculous pericarditis follows hard upon the rheumatic form. In Wells' cases, where the condition was miliary and chronic, there were adhesions and no fluid. In acute miliary eruption, and in those where there was caseous deposit,[1] there was also more or less effusion in the pericardial sac.

In one instance, where no tubercles were shown in a case of acute pericarditis, the inflammation was apparently due to toxins of tuberculous origin. This opinion was supported by the fact that tubercles were found extensively in other viscera. The tuberculous cases, especially those which are acute, result fatally. This seems to be true, also, of acute pericarditis following pneumonia or Bright's disease, but is not true of this complication of acute articular rheumatism.

The forms of tuberculosis as they are found in the pericardium are either of miliary form or cheesy masses. When effusion exists it is serous, bloody, or purulent. It may be moderate or considerable in amount. Whenever the condition has existed for some weeks, it is probable that the pericardial sac becomes softened and dilated, and offers a very insufficient support to the heart. The clinical evidence of this softening and dilatation of the pericardial sac in disease is shown by its greater capacity to contain fluid. Experimentally, this capacity is limited to about 700 c.c. of liquid when forced into the sac.[2] In disease we know much greater quantities of fluid may be contained. Even when these larger amounts are present, we can only recover them in part by paracentesis, owing, as will be shown later, to the position of the heart in the fluid. Soon the heart would show signs of dilatation, and this condition more surely and rapidly occurs if the heart walls are subjected to any increased strain.

In some instances of tuberculous pericarditis, as we know, adhesions with the chest wall have developed. These adhesions, if more than usually taxed, are apt, sooner or later, to be stretched and in

[1] My second case.

[2] Chatin. Revue de Méd., June 10, 1900.

some instances to give way. Under these circumstances the heart shows signs of insufficiency very soon.

As Sequira[1] points out, the dilatation of the pericardium is very important from the standpoint of ultimate prognosis, and this we can readily appreciate when we consider the immediate effects of hypertrophous dilatation where passive congestion of the viscera is more than likely to occur. Sequira's observations are based upon the history of 130 cases of acute pericarditis and observations of 1000 cases.

In occasional instances the pericarditis seems to be due to mere extension from adjacent parts in which tuberculous lesions clearly exist. Under these conditions the pericarditis, curious to say, may occasionally be simply inflammatory. This point is affirmed by Osler. Such instances have also been noted where the extension came from a case of non-tuberculous pleuritis. Likewise they have been recognized as final complications of chronic tuberculous states and as a result of terminal bacteremia (Wells).

In certain instances where the process in the pericardium is an acute one, tuberculosis has not had time to develop there, but later we should doubtless have discovered it if death from other organs affected with tuberculosis had not occurred. Tuberculous pericarditis heals through the formation of fibrous adhesions. In some forms, especially the caseous, the healing may be accompanied with calcification. The thickening of the sac wall may become very considerable. This is true of the parietal wall particularly. These cases are often accompanied with a deposit of numerous miliary tubercles. At the same time there is present more or less effusion, which may present different characters. Often it is distinctly bloody. Still this is not sufficient to determine the diagnosis, as it may take place in other conditions. Of the 11 cases found in literature by Sears,[2] 6 occurred in scurvy, 3 in rheumatism, 1 in goiter, 1 idiopathic, in an alcoholic subject.[3]

Bacilli may be found in this fluid, although sometimes it requires several careful examinations to reveal them.[4] Osler reports 1 case,

[1] British Medical Journal, June 17, 1900.

[2] Boston Medical and Surgical Journal, 1898, p. 298.

[3] Churtan. American Journal of the Medical Sciences, 1892, p. 84; also, Michailoff, loc cit., 1878, p. 278.

[4] Report of my first case.

quoted from Kast, in which tubercles have been found in the pericardial effusion. F. C. Shattuck's[1] second case is another. Where this examination has remained negative the bacilli are revealed solely by means of animal inoculations.[2]

The proportion of successful inoculations is considerable. It is of great value in fixing the positive diagnosis to be made. The drawback to it is the time it takes to develop tubercles.[3] It is in the exudate, as well as in layers of pericardium, that we find tubercle. When it occurs in pericardial layers it oftener affects the parietal one and disseminates to the left pleura. Serous effusion, when present, is frequently surrounded by fibrous exudation, which in places becomes adherent.

The myocardium may be affected with tuberculous infiltration at the same time as the pericardium. The miliary form is relatively unimportant as compared with the caseous. The latter penetrates deeper and sometimes perforates the cardiac walls, and may surround itself with a fibrinous clot.

Formerly primary cases of tuberculous pericarditis were reported. To-day, thanks to a more advanced knowledge of pathology, this erroneous affirmation is rarely met with. One reason is because lesions formerly considered of doubtful nature are now recognized to be tuberculous. Hence, when such lesions are found elsewhere and by their structure are known to be of old date, we can readily appreciate that it is from them that the infection of the pericardium proceeds. In very many cases, without doubt, the infection is carried by the bloodvessels; in others the lymph channels are the evident way of transport.

Simple carrying, as it were, by extension of a tuberculous process through contact, although still admitted, is not so frequently allowed as heretofore. The ordinary development of tuberculous pericarditis is to run a subacute or chronic course. This course may be such an insidious one that for a long while the disease is latent and no obvious symptoms indicate its presence. Indeed, Osler reports only a single case in which, during life, "the diagnosis of tuberculous pericarditis was made with a reasonable degree of probability." If, however, there is no rheumatic history and tubercles are discov-

[1] TRANSACTIONS OF THE ASSOCIATION OF AMERICAN PHYSICIANS, vol. xii. p. 194.
[2] This was true in my second case. [3] About six weeks in guinea-pig.

ered elsewhere, with previous symptoms of pericarditis, we should think of the tuberculous form. The protracted course of the disease and the more marked irregularities of temperature may indicate its presence. Sometimes the symptoms occur, but are concealed by grave symptoms of other organs which are affected from general miliary tuberculosis as well as the pericardium. It is a fact also worthy of remark that, as a result of experimental researches about tuberculosis, while lungs, pleuræ, and mediastinal glands are usually attacked, it is a very infrequent circumstance to find the pericardium involved ; indeed, it is doubtful if there be any well-authenticated cases of it. The involvement of the pericardium through the lymph channels and with transport of tubercle bacilli largely comes from the lungs, pleuræ, and peritoneum. This infection of cardiac lymphatics is doubtless carried on indirectly, so far as the former organs are concerned. Owing to the free anastomosis of the lymph vessels across the diaphragm, it is readily understood how a tuberculous peritonitis may cause directly the development of tuberculous pericarditis. Where the tuberculous pericarditis is of caseous form, brought from mediastinal glands, it is probable that later on this matter is carried to and produces secondary infection of the lungs and pleuræ.

In regard to the question of the frequency with which one layer of the pericardium is affected as compared with the other, this, it appears to me, is difficult of solution, despite the statement of Wells, and, in any event, of no practical moment.

What is affirmed with authority is that a large proportion of cases show tuberculous deposit in mediastinal lymph glands and pericardium at about the same time, and frequently this is true where no tuberculous deposit exists elsewhere. We are more likely to notice this dual condition where already the process has become somewhat a chronic one. Effusion into the pericardium is more likely to occur, it is stated, where caseous masses exist on its surface than where we find the small gray tubercles.

Where the myocardium is affected the disease comes primarily, as a rule, from the pericardium. The muscle of the heart is, however rarely thus diseased. This is especially true of the ventricle; the auricle is oftener invaded.

Tuberculous pericarditis may recover, it is stated. This is rare.

In general, we may say it is not directly fatal, and death subsequently occurs from tuberculous deposit in some other important organ. At this time that of the pericardium may have become quiescent. This, of course, occurs only in the relatively chronic forms. If it does, we may find fibrous nodules in the exudate or pericardial walls as the only direct evidence of a tuberculous lesion. It may be inferred, however, by considering the evident tuberculous condition of the mediastinal glands, and through the fact that this is the sole efficient cause of tuberculous pericarditis which can be brought to light.

The most important effects, clinically, are those which are seen upon the heart. In some instances there is no valvular lesion or structural defect of the heart muscle, and yet there is dyspnea, cyanosis, and weakness of pulse—all pointing to cardiac distress. The effusion by its mere pressure seems to be the explanation of these symptoms, and its prompt removal is, therefore, the essential and urgent indication, so as to re-establish, as far as may be necessary, functional power. If this condition is allowed to remain, even though life may not be imminently imperilled, the heart soon shows the results of the external pressure against which it contends by becoming enlarged with hypertrophous dilatation, and by growing weaker progressively and constantly. Where adhesions exist with the thoracic walls, which is often true in these cases whenever they tend to chronicity, the duration of life is notably shortened. It is equally true, only more so, where the two layers of the pericardium have also become adherent and the effusion has become resorbed or been removed by paracentesis. In these instances life may be measured by a few months. This is eminently true in pericarditis affecting children. Lee Dickinson[1] reports "one solitary case in which adhesion, certainly contracted in childhood, proved ultimately harmless." The late Dr. Sturges showed in these cases that acute carditis is present, usually of rheumatic origin. Peck[2] has ably described in several such cases a condition of "pericarditic pseudocirrhosis" resembling precisely the *mixed form of cirrhosis*[3] of the liver, which is due to a latent pericarditis. The

[1] American Journal of the Medical Sciences, 1895, p. 692. [2] Ibid., 1896, p. 221.

[3] A case of pseudoatrophic cirrhosis of the liver, secondary to adherent pericardium, is reported by Dr. R. H. Babcock, of Chicago, in the Medical News, December 14, 1901, p. 924.

differential diagnosis is based upon: (1) Absence of etiologic factor of cirrhosis; (2) a history of pericarditis supported with the evidences of it from physical signs.

We should not ignore the difficulty of explaining why pericardial adhesions are ocasionally followed by such changes. Wells gives several good and sufficient reasons why tuberculous synechia is less to be feared than that which occurs in purely rheumatic cases. Among these may be regarded slowness of growth, no valvular defects, no toxemia affecting heart muscle. Moreover, he states heart dilatation occurs in rheumatism at period of inflammation or later, when effusion is being absorbed.

In the latter instance, as I have already pointed out, the pericardium becomes dilated and softened, and thus fails to give the heart proper support. In addition to this, however, if the pericardium is attached to the chest walls it simply cannot follow the heart, owing to mechanical conditions. For this reason, again, the heart yields more and more to internal pressure, and consequently becomes more and more dilated, weak, inefficient, and ultimately powerless.

In these cases we often find beneath a very thick pericardium a considerable growth of connective tissue, together with a deposit of fat in the superficial parts of the heart muscle.[1] In rare instances are we able to demonstrate the existence of gray tubercles in the myocardium. Where caseous deposits are found at the autopsy they are more important because they have penetrated the heart wall deeply, and in the event of perforation they serve to explain the transport of numerous bacilli in other organs and the signs of general miliary tuberculosis, which were easily recognized, even during life.

The usual termination of tuberculous pericarditis is death. This may be brought on directly by the recurrence of a large effusion, frequently hemorrhagic, which repeated tapping has failed to relieve. Of course, at times the adhesions which have formed to chest walls, lungs, and diaphragm seem greatly to shorten the duration of life; but these again may never occur, and the heart may simply float freely in the fluid which surrounds it more or less on all sides.[2] Often, as I have said, the fatal ending is immediately attributable

[1] Second case reported by me.

[2] See my first case—pathologic report.

not to the heart itself, but to the general miliary tuberculosis of different viscera with which the cardiac condition is associated.

Death may occur from an embolism, but this is extremely rare.[1] "Tuberculous pericarditis is generally unaccompanied by any symptoms referable to the heart, and is almost always an autopsy finding."[2] With this statement of Wells, corroborated by Osler,[3] judging by my two recorded cases, I should be inclined to differ.

For the cases which are slowly and insidiously developed there is little or no local treatment to be advocated. This is true of the cases which terminate in synechia and where the symptoms are frequently very obscure. The systolic retraction of the nipple in these instances is a deceptive sign, as more than once I have been able to observe. In this connection Lee Dickinson states we may have pulling in of lower ribs with systole, but adds that cases with this indication are seldom available. The most characteristic of all indications "are rapid progress of the case to the fatal end and the signal failure of all known means of relief in heart disease."[4]

Inasmuch as there is small effusion and no obvious inflammation, these two conditions may not require active interference. In those instances in which the onset of the disease is acute it is indicated at first to limit the amount of inflammation. Personally, I favor the local use of poultices or hot flannel stupes. To the former mustard may be added; the latter may be sprinkled with turpentine. Equal parts of soap liniment and turpentine applied for several hours on warm flannel are recommended. If cold be employed I much prefer Leiter's coil to an ice-bag. The latter is difficult to keep in place and causes distress from cold at times, which we cannot regulate easily.[5] A small quantity of morphin hypodermically may be called for to allay pain. In the cases that I have seen I have not thought the cautery or blisters were required in the beginning of the attack. Later, I am confident, repeated small fly blisters may limit the amount of the exudate formed. It is also possible that an effusion already formed may thus be made to disappear, in part or wholly, and more rapidly than it otherwise would. Despite what has been said, it is far wiser in many cases not to attempt to

[1] Case 8, reported by Wells. [2] Loc. cit., p. 1458. [3] Already cited.
[4] American Journal of the Medical Sciences, 1896, p. 696.
[5] Of course, we can put a towel or flannel compress underneath.

influence the pericardial condition by any local application. Whenever the effusion becomes considerable or excessive, paracentesis should be thought of. If the lips and fingers become cyanosed—if there is marked dyspnea, and weak, frequent, irregular pulse—prompt withdrawal of fluid is necessary to preserve life. If, before paracentesis is performed, the exploring needle shows the presence of pus, it is more judicious, in many instances, to incise the sac freely and introduce a drainage-tube. Of course, if the condition of the patient is imminent, paracentesis may first be performed and subsequently the more radical operation.

The position of the heart with respect to pericardial effusions is frequently undetermined. In purulent fluids the heart is supported by or floats upon the fluid, and is carried directly against the chest walls. This has been proven experimentally. In fluids containing some blood, or in pure serum, the heart is surrounded by fluid, as a rule, of which the larger quantity is in the lower and left lateral portion of the pericardial sac.

Whenever puncture of the heart is indicated, some hesitancy arises in performing the operation on account of the danger incident thereto. There is risk of wounding the mammary artery, of entering the left pleural cavity, of puncturing the liver, of wounding the peritoneum, or, indeed, of going through the diaphragm. Perhaps the latter is of no special moment, as it is the way by which entrance to the pericardium is occasionally suggested or taken by the surgeon in a radical operation.

The classical site for aspiration of the pericardium may be regarded as the left fifth interspace, near the sternal margin.[1] Other regions, however, have been tried more or less successfully—*i. e.*, beyond the left nipple and near the outer line of cardiac dulness; in the right fourth intercostal space; in the angle of the xiphoid cartilage and the margin of the left costal arch. The right interspace is specially indicated by Dr. Rotch, of Boston, in those cases where he has found dulness over this area.[2] Dr. F. C. Shattuck, in his able paper before the Association of American Physicians,

[1] Roberts states (Trans. Surg. Assoc.) that this point of election "will not assure safety to the pleura."

[2] The clinical conclusion from Damsch's experiments was that "first sign of pericardial effusion would be area of dulness in heart-liver angle, as taught by Rotch." (Loc. cit.)

Washington, 1897, has tried different points for aspiration of pericardium, with satisfactory and sterile results.

On one occasion where a small quantity of fluid was withdrawn, later the autopsy showed at least one pint of fluid in the sac. It may be inferred in such cases that the fluid thus discovered was produced during the agony or after death. It seems to me more probable that it was in the pericardial sac during life, but could not be aspirated, on account of the position of the heart and the wrong point of puncture. In this connection I am glad to be able to refer to a recent able article by Dr. O. Damsch,[1] which settles definitely, it may be, most points hitherto questionable about the position of the heart, that of the effusions, and the point where we should always try paracentesis. Dr. Damsch made injections experimentally into the pericardium, the subject being in the upright position, for the purpose of determining the position assumed by the pericardial exudate. *Small amounts*, he found, collect in the lower and anterolateral portions of the pericardium, causing approximation of the right anterior portion of the pericardium to the chest wall. The heart, when of *normal size*, was always found pressed against the posterior portion of the pericardium, the fluid occupying the anterior portion. In cases in which the heart was hypertrophied it was pressed *upward* and *anteriorly*. Its increased size, according to Damsch, causes it to fill the whole space between the anterior and posterior chest walls, and, therefore, since the fluid collects in the lower part (pericardium), the heart must be pressed upward. "From his experiments he decides that the best position *for puncture* is well down toward the lower part of the pericardium." He also decides that puncture in the fifth or sixth intercostal space (left) next to the sternum, directing the trocar somewhat inward, is the safest method and location of paracentesis. Thus performed there is no danger of wounding either heart or pleura. If the heart is normal the fluid is in front of it and at lower part of pericardium; if the heart is *enlarged*, which it usually is, it is floated *upward* and *out of danger*.

Aspiration of the pericardium relieves, without doubt, for a while imminent symptoms, and, as an operation of urgency, should be

[1] Gould's Year-book, 1901, pp. 178, 179.

employed unquestionably. When we come to consider it as a curative means it is of less value. I have seen the fluid recur several times after it has been removed, and that, too, in a relatively short period. This statement is true of instances in which the pericarditis, either at that time or subsequently, was known to be tuberculous. One is thus led to ask whether in these instances it is not preferable to perform a radical operation with proper surgical technic and thorough drainage of the pericardium. In purulent cases the general consensus of good surgical judgment is to that effect. In tuberculous cases where the effusion is not purulent it may be also a wiser procedure than simple puncture, because through the open wound the finger may be introduced and large masses of fibrin extracted. These masses, if allowed to remain *in situ*, inevitably delay cure by allowing fluid to reform rapidly. After a reproduction of fluid on one or several occasions, adhesive pericarditis may and does develop, and, sooner or later, we have to do with a seriously crippled heart. There might be a chance of obviating this by means of the canula left in place and the use through it of some form of alterative injection. Rendu[1] reports such a case of cured tuberculous pericarditis. The modifying injecting fluid employed by Rendu was a solution of pure camphorated naphthol.

What is true in cases where effusion has been withdrawn as regards some of the results to heart fiber is true where we leave the fluid in the pericardial sac and do not attempt to remove it. By and by underneath the thickened layer there comes a large layer of fat. This fat finally penetrates the heart wall between the muscular fibers, and, in connection with a deposit also of cellular tissue, leads to fatty degeneration of the heart structure, and later, perhaps, to combined fibroid changes.

As regards serous effusions, even though large in amount, such as we meet with as a complication, especially of acute articular rheumatism and occasionally in nephritis, these rarely require puncture, in my judgment. Whenever the indication arises, unless the condition be very imminent, I am of the opinion that one or a succession of fly blisters over or near the heart will accomplish all that is urgently required. It is not essential, moreover, that much fluid

[1] Journal of the American Medical Association, 1901, p. 1432. Also, Bull. de la Soc. des Hôpitaux de Paris, March 21, 1901.

be removed from the pericardium in these cases so as to promote absorption ; a small quantity is sufficient. The proof of this is that often after aspiration of the pericardium, where very little fluid has been actually removed, a notably beneficial effect quickly follows. The same thing results from a severe counterirritant or revulsive. How this acts (blister[1]) I am not quite sure. Evidently there is no immediate vascular connection between the skin in the precordial region and the heart itself, and for this reason it would seem as though the blister would do as much good were it placed over a region far removed. Certainly, if mere reflex action comes into play it is possible. And yet, somehow or other, I am a believer in its good effects applied over the precordium, and I do know that revulsion, irritation, or heat locally over the heart is of great practical value in adding to its power. I can readily conclude, therefore, that wherever effusion in large amount is partly passive, increased heart action may be remedial in a very distinct and rapid manner.

With respect to the operation of paracentesis *versus* the use of counterirritation in those cases where the effusion is limited and probably serous, we should always have in view the possibility of change to a purulent effusion caused by the little operation itself, especially if performed with the ordinary trocar and canula. With proper aseptic precautions and the use of the aspirator, this to-day may be regarded as a negligible quantity. Moreover, it is known that but one case has resulted fatally following the puncture. "With this exception, all the patients were greatly relieved by the removal even of a small amount of fluid, and many recovered completely who probably would have died if the operation had not been performed." [2]

In purely purulent effusions it is now generally admitted that surgery with open wound, with or without drainage, should alone be considered. Porter's case[3] and others still prove this. Only lately, for example, H. Lilienthal has had a successful radical operation in a case of purulent pericarditis. Here aspiration had proved insufficient. In Lilienthal's case a portion of the fifth left costal

[1] Dr. Shattuck never uses blisters. Drs. Tyson and Rotch would not let them go.

[2] American Journal of the Medical Sciences, 1897, p. 458.

[3] The only case ever treated by incision in Massachusetts General Hospital (F. C. S.). Boston Medical and Surgical Journal, May 6, 1897, p. 438.

cartilage was resected close to the sternum under local anesthesia. Forty ounces of fluid were removed from the pericardial sac.[1]

In another case, reported by Ogle and Allingham, the pericardium was opened, a large quantity of pus removed, and the pericardium cleansed, without interference with the action of the heart and with decided benefit to the patient. It was shown in this instance that the heart can be handled without harm. It is therefore advisable to treat these cases precisely as we would an empyema. Indeed, the operation is more indicated than that of empyema, because the walls of the cavity are better able to contract and finally lead to complete obliteration. We know the outcome in empyema, where, to reach the best obtainable result, portions of several ribs must often be resected. Even then we have to deplore many incomplete successes.

Finally, in the operation by opening and drainage we have really the only legitimate hope of entire recovery. No one has insisted upon this operation more strenuously than Dr. J. B. Roberts since 1876. In a late paper he reiterates his findings. Very properly he says, "the diagnosis of the purulent character of the effusion was only determined by exploratory puncture."[2] And "this should be done at the upper part of the left xiphoid fossa close to the top of the angle between the seventh cartilage and the xiphoid cartilage."[3]

"The prognosis is good," says Dr. Roberts, "in pericardotomy for pyopericardium. In a table of 26 collected cases 10 recovered and 16 deaths were shown. This gave a percentage of recovery of 38.4. Of the fatal cases at least 9 were septic, and all the others who died had complicated lesions, such as pleuritis, or pulmonary, cardiac, or renal lesions."[4]

"The results obtained by incision and drainage in tubercular peritonitis suggest that drainage in tuberculous pericarditis may lead to a permanent cure. The ease with which the pericardium can be irrigated with solutions of iodoform would seemingly add to this probability of success."[5]

After analyzing different cases, Roberts writes: "These observations and other reported cases not here mentioned have almost con-

[1] New York Medical Record, November 25, 1900.
[2] Boston Medical and Surgical Journal, May 27, 1897, p. 522.
[3] Loc. cit.
[4] Loc. cit.
[5] Transactions of the American Surgical Association, 1897, p. 108.

vinced me that incision is better than aspiration, even in cases not supposed to be purulent. It establishes diagnosis in dubious cases, avoids cardiac injury, saves the pleura from puncture, affords complete evacuation of effusion, permits extraction of thick pus and membranous lymph, and gives opportunity for disinfection of the sac when that is necessary." [1]

Porter cites one successful case of incision in serous pericarditis where puncture failed to relieve.[2]

Personally, so far as tuberculous cases are concerned, I agree with Dr. Roberts. Ordinarily, in cases of simple serous effusion of other provenance I do not believe incision is called for, and if any operative interference is required I still prefer paracentesis. If irrigation be employed as an adjunct in incision the outflow of fluid must be unimpeded, or death may rapidly result from it.

In regard to the technic, it is not necessary to say more than to point out that the best operation is the one usually which permits best drainage in a given case. In one instance it may indicate resection of the fourth or fifth rib on the left side; in another the pericardium should be opened from below and through the insertion of the diaphragm near the central tendon.

It should be remembered, in my judgment, that the question of radical operation for pericarditis with effusion is different in one very important particular from that of pleurisy with effusion. There are two lungs; there is only one heart. A patient may do fairly well a long time with pleuritic adhesions, a retracted chest wall, and an atelectatic and fibroid lung. No patient will continue long to be in any degree comfortable or active who has adhesive pericarditis as a sequela of large and long-continued effusion, with the pathologic changes of heart walls which invariably follow sooner or later.

To those who have had small clinical experience with these cases and who may be led to believe that the liability of heart puncture is slight, I would point out that the anatomic relations of the pericardial sac, despite Dr. Damsch's researches with the chest walls and left pleura, in many instances are very perplexing and variable. As to the differential diagnosis of pericardial effusion with a heart

[1] Loc. cit.

[2] Transactions of the American Surgical Association, vol. xv.

merely enlarged, while this is often very simple and requires no great medical acumen, there are occasions when the most careful use of physical methods of exploration will leave one in a state of great uncertainty. Again, I have had to do with cases where I was confident there was a large effusion and no risk in introducing a small trocar connected with the aspirator. Unfortunately, my diagnosis was incorrect, manifestly on one occasion, and instead of withdrawing fluid from the pericardium my aspirating needle penetrated the heart wall. This was obvious by reason of the fixed position and special movements transmitted to the canula when the trocar was withdrawn. In this instance no great or immediate harm resulted. Still, it is an accident to be avoided, as far as possible, by great care and attention.

Orphüls reports a case where, at the autopsy, the end of a trocar needle was found in the scar tissue at the upper portion of the interventricular septum. This needle probably broke off in an exploration or in a previous operation of paracentesis.[1] Loison[2] affirms, also, that in wounds of the heart and pericardium the "prognosis is not always grave." This judgment is strengthened by the statistics collected both by Fischer and himself. On the other hand, Rotch has "known of a case where pricking the heart with an aspirator needle caused sudden death," and Janeway one where the aspirating needle tore the heart, causing death.

Formerly, so as to avoid just such mishaps, I had constructed for myself a modified Roberts canula.[3] This is a very good instrument when kept in proper order. It is a little complicated, however, and requires to be looked after. All that precedes acquires additional interest if we recognize, as many do, that the ordinary medicinal remedies as applied to the treatment of pericarditis with effusion (especially the tuberculous form) have very little value.

I am not aware, once pericarditis has become developed, that any remedy given internally abridges its duration or changes its course very perceptibly. I acknowledge, of course, in a few instances, that the heart needs special stimulation in view of the failure that may come on suddenly or by degrees. The alkaline treatment may prove

[1] British Medical Journal, January 27, 1900.
[2] American Journal of the Medical Sciences, 1900, p. 218.
[3] Medical Record, March 29, 1884, p. 361.

very useful in giving strength to cardiac contraction—more, indeed, than the use of digitalis. This would be in accord with the experiments of Gaskell.[1] I also know that in a few—a very few sthenic cases—aconite may be indicated for a short time to lower blood tension and decrease the rapidity of the pulse; but that is about all there is to do in the acute stage by way of the mouth. Locally, as I have already pointed out, the ice-bag or poultices and blood-letting (leeches and cups) are useful where there is pain or great increase of heart action. Beyond some degree of soothing or quieting thus produced, we should not count upon a great return. The prophylactic measures to be employed have to do solely, it seems to me, with the efficient causes of tuberculous pericarditis which prevail, be it possibly pleurisy, pneumonia, sepsis of some sort, or mere exposure, fatigue, or debauch.

As we know already, tuberculous pericarditis may show itself when we have had little or no suspicion of its presence. It may also be ushered in with so few obvious symptoms or signs, local or general, that except in an accidental way it is not discovered during life. There are many examples, indeed, where the presence of the disease was ignored during life and only ultimately revealed by the findings at the autopsy.

Appended is an abstract of the history of my second case:

History of Case of Tuberculous Pericarditis (No. 2). B. F., married, a hod-carrier, born in the United States, aged thirty-eight years, was admitted to St. Luke's Hospital under my care, March 19, 1901. Family and personal history negative, save that he was a somewhat excessive drinker of beer and whiskey. Present illness began four months ago, after a debauch, with pain in his right side. No cough, chills, or vomiting. The pain in the side lasted a month, when he began to cough, expectorated blood-stained mucus, had some fever, with afternoon exacerbations, and became weaker. Two weeks ago pain in the precordial region, with palpitations, developed; also at times dyspnea. No swelling of the feet.

Physical examination shows marked increase of cardiac dulness, rapid heart action, and a high-pitched systolic murmur, heard between the nipple (left) line and sternum. Thoracentesis gave

[1] American Journal of the Medical Sciences, 1896, p. 696.

serous fluid in right pleural cavity. Temperature, 99.3° F.; pulse, 100; respiration, 49. Urine: acid, 1020, no sugar, no albumin, few leukocytes. No tubercle in sputum.

X-ray examination shows shadow corresponding to line of cardiac percussion dulness.

Microscopic examination of blood negative; also examination of eyes negative.

April 25th. Guinea-pig inoculated with fluid from right pleura. On May 19th tubercle found in cheesy pus from enlarged lumbar glands of guinea-pig.

May 26th. Patient paralyzed on right side. Soon became comatose and died the same day. During sojourn in the hospital the patient was feverish, with pronounced irregular rise in the afternoon.

Autopsy, made by Dr. N. E. Ditman, resident pathologist, showed much thickened pericardium; sac contained eight ounces of yellow, turbid fluid. Heart enlarged, muscle pale, and covered by a layer of subpericardial fat; valves normal, save a slight atheroma of one flap of mitral. Lungs, liver, spleen, meninges, and peritoneum showed disseminated miliary tubercles.

Microscopic examination showed cheesy degeneration and numerous giant cells throughout the pericardium. In the layer of fat over the heart and beneath the pericardium were numerous small masses of small round cells, and in each mass giant cells were present. The heart muscle, superficially, was infiltrated with fat. More deeply there was a moderate small round-celled infiltration between the muscle bundles, and in places the latter are separated by connective tissue; connective tissue of bloodvessel walls increased in amount.

A CASE OF MENINGEAL HEMORRHAGE AND NEPHRITIS SUPERVENING UPON A PURPURIC DIATHESIS OF TWENTY-FIVE YEARS' DURATION.

By ROBERT T. EDES, M.D.,
of Boston.

The following case, although one of a by no means rare disease, is sufficiently unusual in its termination to be worth putting on record, and, besides, from the length of time it was under partial observation, makes interesting some of those slighter symptoms which may persist for years, and yet are forgotten when greater pathologic disturbances have furnished the opportunity to suggest an explanation. *Purpura* (*peliosis*) *rheumatica* has been considered more or less akin to both the conditions involved in the name, being usually and correctly arranged in the text-books as a subspecies of purpura. The present case appears to be most correctly classed under this head, although without the urticaria and, until near its termination, without the erythema which mark the more typical cases. It was distinguished on the one hand from the almost trivial "purpura simplex," and, on the other, the much severer "purpura hæmorrhagica," by the presence of pain, usually in the joints—though not always those joints having the most eruption—and the absence of hemorrhages from the mucous membranes. The hemorrhagic tendency in purpura has been naturally ascribed both to some morbid but unknown condition of the blood, and also to a greater permeability or fragility of the vascular walls. Anemia is often spoken of in this relation, but in this case the blood was of full color, as compared with Tallquist's standard color scale, which, it seems to me, is quite as accurate for practical purposes as Fleischl's and far more convenient. Neither did the "smears" or "wipes" show any marked departure from the average, not even any poikilocytosis, so that,

although no corpuscular count was made, it is fair to say there was no anemia.

There was evidently a greater fragility of the vessels or less resistance to mechanical injury, as was shown by the appearance of the hemorrhages—which were on the average a little larger than petechiæ, if this word is to be limited strictly to the "pinpoint"—at places exposed to pressure or movement.

On one occasion there were spots both in front and behind the knee-joint, but not on its sides—that is, in the regions where from the flexure and extension of the limb the skin was subject to more stretching and compression. Frequently, however, as happens in most cases of the kind, no very definite connection could be observed between the localization of the hemorrhages and any special pressure. If we take into consideration the evanescent character of the cutaneous lesions, the seeming capriciousness of the distribution of many of them, and their very common association with urticaria and erythema, there is good ground for suspecting in most cases of this kind not only the strength of the walls of the skin vessels, but their vasomotor supply.

Mrs. ——, aged forty years, of slender build, delicate, but not an invalid, twenty-five years ago (1876) had an attack of purpura, of which I have no further notes. In April, 1882, she was somewhat dyspeptic and run down. She had severe pain in her left hand, which was swollen. There was some pain in other joints and purpuric spots on the legs.

In 1883 the urine, of specific gravity 1026, contained a very few casts, but no sugar or albumin.

In 1885 there was a tendency to diarrhea, nausea, and headache. In December of the same year there were several hours of glittering before the eyes and seeing of only one-half of things. Rather weak.

In April, 1887, there was nausea, the face was swollen for some time, but no swelling of hands or feet. An undated note says that many years before she had had her face (and hands?) puffed up with a single dose of arsenic.

In 1897 there was sore-throat; red, with no exudation. Pain in the wrists, but no petechiæ, ecchymoses, edema, or redness. In June, urine 1029, with crystals of calcium oxalate and uric acid, but otherwise normal. Less pain and no petechiæ. In December of the same year there was pain in the great toe, which grew pink and then black under the nail. Diarrhea; slight bloody discharges. Temperature normal; very slight twinges of pain.

On December 19, 1898, digestion out of order; "full of rheumatism." Joints puffy, but no spots discovered.

In April, 1899, not very well; not decided dyspepsia; attacks of hemianopsia; very slight vertigo; "floating feeling." In December, uric acid.

In July, 1900, there was an attack of vertigo and hemianopsia, with some gastric and cardiac disturbance and headache. Urine was normal. This condition improved during the summer, but a "floating feeling" lasted until October. The urine at this time contained no albumin but a few casts.

In September, 1901, not very strong. In November there were localized and painful swellings at various places, which did not last. There were several ecchymoses about the ankles. A "wipe" of the blood gave no indication of anemia, nor did it differ as regards the character or proportions of the corpuscles from the normal. Salicylates were given for about six days; after this iron. The urine was of specific gravity 1021, without albumin, but having in the sediment some blood and a very few small transparent casts, with a few uric-acid crystals.

Throughout December and January the same general condition continued with slight swellings at various places, leaving either nothing behind them or a discoloration like a bruise. Usually there would be distinct spots of varying sizes, but never more than a few millimeters in diameter. They lasted from a few hours to a day or two. On one occasion edema around one ankle lasted for a number of days. There was occasional diarrhea—never severe and never lasting—with no hemorrhage from the bowels. The pulse was increased in frequency, but not in excess of the normal. There was no fever, and the general condition did not materially change except in the way of gradually increasing weakness. The blood retained its normal character, but, unfortunately, there was no examination of the urine during January, the last examination in December having shown neither casts nor albumin, but urates and uric acid.

On February 3d she had a cold with a tickling cough, such as she had had several times before. It was attended with no physical signs, and the temperature a few days later rose only to 99° and 99.8°. There was some pain about the joints, with edema of the feet and ankles. The urine was considerably less in specific gravity (1008 to 1011), and contained from this time on constantly more or less albumin with casts and a little blood. On the 12th there was headache on the left side and vomiting. On the 16th, the pulse having been a little higher (84) and the temperature from 99° to 100°, she was dressing, with the intention of returning to her home; but before leaving the room she complained of not being able to see, and had a convulsion, in which she became cyanosed and passed urine involuntarily. On the 17th, very severe headache, complained of for the first time, and a convulsion, with succeeding delirium. On the 20th two convulsions with delirium. At about this time there were appearances looking like hemiplegia, which continued with varying intensity until death. She lay most of the time with the head turned slightly to the left, and looking toward the left. She could use either hand, but it seemed preferably the left. The forehead wrinkled alike on both sides, although a little later her friends said that she smiled only on one. She spoke but little and indistinctly, but there was no paraphasia. On the 20th she put her finger on her tongue and said

"pallyzed." On the 25th there was an eruption all over the back, somewhat resembling scarlatina, though not so bright red.

On March 6th she died. For ten or twelve days before death the urine averaged about one liter *per diem*, of specific gravity from 1008 to 1011, always with a considerable amount of albumin and casts of various kinds, except the waxy and those large ones composed entirely of degenerated epithelium; also usually uric-acid crystals.

The autopsy was made eight hours after death occurred.

The thoracic and abdominal organs showed no decided abnormality except posterior congestion. The heart muscle was firm. The kidneys were of normal size and not wrinkled or puckered or cystic, but the capsule was in places very slightly adherent, this being the only indication of any interstitial nephritis.

On removing the scalp the calvarium was found stained with a dark-red, sharply defined patch of color, extending forward with a curved convex outline two-thirds of the way from the nucha to the frontal eminence on the left and one-third on the right. The surface of the left hemisphere was more congested than the right, over a region not exactly corresponding to the blotched appearance of the calvarium, but having its greatest intensity over the posterior portion of the second frontal convolution. At this point, between the ascending frontal and second frontal, was an irregular black clot, as large as a chestnut, molded into the sulci. The surfaces of both these convolutions were eroded and softened. On the right side, at the posterior extremity of the first occipitoparietal convolution—or perhaps a little further from the median fissure—at about the point marked P2′ on Ecker's diagram—was a similar clot, but smaller, and having eroded the surface of the convolutions somewhat less. No other lesions were discovered.

The exact point of origin of the hemorrhage was not determined, but from its situation and the large size of the superficial dilated vessels found immediately over it, it seems more likely to have been venous than arterial.

There are several points of interest in this case in connection with both pathology and therapeutics, not conclusive, to be sure, in regard to anything, but suggestive, as so many of our purely clinical facts must be. Of the former is the relationship to rheumatism, as shown by the pain and swelling existing at the same time as the petechiæ, but not always at the same place, and, on one occasion at least, where there were no petechiæ anywhere. On the other hand, the dissimilarity to rheumatism in the complete integrity of the heart and the absence of atheroma, notwithstanding the long existence and the repeated attacks for years, of which, I dare say, there were more than appear upon my notes.

After the convulsions had occurred, and in the presence of albumin

and casts, the diagnosis of uremia was certainly a very probable one, and the suggestion of a chronic interstitial nephritis, with but few symptoms, and leading up either to the acute attack of nephritis or to the unsuspected outbreak of uremia was made. This, however, was highly improbable in face of the examinations which had been made over many years, and showed but little abnormal, except an occasional excess of urates. That chronic interstitial nephritis without urinary symptoms, which occupies so important a place in many articles, is, in my experience, more often talked about than seen.

The existence of acute nephritis was, of course, indisputable, but its importance as the cause of the convulsions was doubted when the urine continued to be secreted in abundance at the rate of about one liter on each day up to within a day of death, and of a specific gravity (1008 to 1011), which, although below normal, was undoubtedly capable of taking care of all nitrogenous waste from the limited diet that was used. The autopsy fully confirmed this view.

Meningeal hemorrhage without cerebral hemorrhage and without arteriosclerosis is certainly an unusual occurrence in chronic nephritis. It may also be said to be rare in this form of purpura, in which there are usually, as in this case, no hemorrhages from mucous membranes.

Looking upon the clot in the motor region of the left side as the source of the right-sided hemiparesis, the interesting inquiry arises whether the other clot had anything to do with the recent defect of vision and also with a possible tendency to congestion of the same neighborhood, existing for many years. Unfortunately, the notes do not state the side of the earlier hemianopsia and the glitterings before the eyes. Also, the lesion, as found at the autopsy, is situated too far out to have been the seat of the distinct limitation of the visual field, although it may very probably have been connected with the last failure of vision, the nature of which the patient was unable to describe more accurately.

ON ADRENALIN GLYCOSURIA AND ALLIED FORMS OF EXPERIMENTAL GLYCOSURIA DUE TO THE ACTION OF REDUCING SUBSTANCES AND OTHER POISONS ON THE CELLS OF THE PANCREAS.[1]

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THIS publication is made for the purpose of giving a condensed account of a recent experimental research on glycosuria due to the action of various poisons on the cells of the pancreas. A detailed account of this work will, before long, be presented in the *Journal of Experimental Medicine.*

The starting point in this study of glycosuria is the observation that adrenalin chlorid, when introduced into the peritoneal cavity of dogs, is almost regularly followed by the appearance of considerable quantities of sugar in the urine.[2]

Preparation and Chemical Characters of Adrenalin Chlorid. Of the method of preparing adrenalin chlorid little need be said here, as this subject has recently been discussed by Takamine.[3] One point should, however, be noted: In the course of preparing adrenalin the finely disintegrated suprarenal glands are steeped in water for about five hours, at a temperature varying from 50° to 80° C., and later are exposed to 90° to 95° C. for one hour. This temperature is sufficiently high to destroy most, if not all, diastatic ferments.

[1] This study was aided by an appropriation from the Rockefeller Institute for Medical Research.

[2] Herter and Richards. Notes on the Glycosuria following Experimental Injections of Adrenalin. The work of Blum and others is here mentioned. The Medical News, February 1, 1902.

[3] Journal of the American Medical Association, January 18, 1902.

The adrenalin chlorid (in concentration of 1–1000) of commerce shows a slightly alkalin reaction on moist litmus-paper and with phenolphthalein. The colorless aqueous solution absorbs oxygen from the air, and changes to pink and later to red or brown. The energetic reducing action of the solution is shown by its behavior to many salts. One cubic centimeter of 1–1000 aqueous solution of commercial adrenalin chlorid (containing 0.5 per cent. of chloreton) reduced 4.2 c.c. of Fehling's solution, and 100 c.c. of the solution were thus equivalent to 0.21 gm. glucose. Adrenalin chlorid reduces potassium permanganate in the cold, and Dr. Wakeman has calculated that the weight of oxygen which is taken up from this salt during the reduction of 1 c.c. of the commercial solution of adrenalin is 0.000313 gm.[1]

The commercial aqueous solution of adrenalin (1–1000) was employed in the research to be described.[2] A few observations were made with adrenalin, prepared by a somewhat different method, by Dr. John J. Abel, who kindly placed some of his product at our disposal. One portion of the adrenalin, given us by Dr. Abel, is free from loose ammonia, and differs slightly in some of its reactions from the adrenalin of commerce.

There are many conditions which affect the degree and duration of adrenalin glycosuria, and some of these must be mentioned.

Mode of Administration. Subcutaneous injections of adrenalin chlorid yield only slight degrees of glycosuria. Thus, in a typical instance, a dog, of 15 kilos, received 10 c.c. adrenalin under the skin. Before the injection the urine contained 0.48 per cent. reducing substance (Pavy's method). The first collection after injection contained 0.66 per cent. reducing substance; the second, 0.52 per cent. reducing substance. The explanation of the small excretion of sugar is that the adrenalin is largely oxidized before entering the circulation. Larger percentages of sugar may be obtained, but they involve the use of larger doses.

Intravenous injections of adrenalin are followed by a larger excretion of sugar, where a dose of from 5–10 c.c. of adrenalin is put into a dog of from 8–15 kilos. Five or six per cent. of glucose may be observed under these conditions, but the percentage is sometimes

[1] Using a standard solution of $KMnO_4$ in which 1000 c.c. of the solution = 0.8467 gm. $KMnO_4$.

[2] When not otherwise specified this solution is meant when adrenalin is mentioned.

much smaller. A rise in the blood pressure is an accompaniment of the glycosuria, but the latter outlasts this rise.

Other conditions being similar, a given dose of adrenalin (from 2–15 c.c.) gives rise to a greater excretion of sugar when administered by the peritoneal cavity than when given intravenously. In well-fed dogs, of medium size, a dose of from 4–6 c.c. is always, or nearly always, followed by some degree of glycosuria. Somewhat larger doses almost regularly occasion the appearance of from 3–6 per cent. of sugar within an hour of the completion of the injection. The percentage of sugar may rise to 10 per cent. or more. Sugar has, in some cases, been detected within fifteen minutes of the completion of the injection. The systemic blood pressure has been observed to rise after intraperitoneal injections, but not to the height noted after intravenous infusions. Thus, in a dog of 11 kilos there was a rise from 100 mm. to 110 mm. of mercury after an injection of 10 c.c. of adrenalin. Some rise was maintained for about an hour. Then there was a fall to below 100 mm. Under similar conditions an intravenous dose of 10 c.c. of adrenalin might be expected to cause a rise from 100 mm. to 130–160 mm. of mercury.

By mouth, adrenalin apparently has no effect in ordinary doses. A well-fed dog of 13 kilos received 10 c.c. of adrenalin by mouth without resulting glycosuria, an experience which corresponds with the known absence of physiologic effect of gland extracts upon the human subject. It is possible, however, to induce glycosuria by giving very large doses of adrenalin by mouth. Thus, while a dog of 8 kilos received 20 c.c. of adrenalin solution without the appearance of sugar in the urine, another dog, of nearly the same weight, showed a glycosuria of nearly 1 per cent. after a dose of 30 c.c. Neither of these dogs exhibited any symptoms.

Effect of Dilution. In the case of intraperitoneal injections of adrenalin the excretion of sugar appears to be comparatively small when a considerable degree of dilution is practised. Thus, in a well-fed dog of 8 kilos, 10 c.c. of adrenalin with 40 c.c. of 0.85 per cent. salt solution, gave rise to the appearance of 0.16 per cent. of sugar in 1000 c.c. of urine, a much smaller glucose total than is usual following such a dose. Sometimes, indeed, glycosuria does not appear, as, for instance, in the case of a well-fed dog of 6 kilos which received 4 c.c. of adrenalin with 12 c.c. of 0.85 per cent. salt solution. Four

hours and nineteen minutes later 30 c.c. of urine contained no sugar.

Size of the Dose. Within certain limits the quantity of sugar excreted appears proportional to the dose of adrenalin, but the relationship has not yet been carefully studied. It is certain that doses smaller than those usually employed may suffice to induce glycosuria. Thus, in a dog of 5.5 kilos an injection of 2 c.c. adrenalin with 2 c.c. of 0.85 per cent. sodium chlorid solution was followed by the appearance of 3.75 per cent. of sugar in the urine. There is reason to think that when a certain dose is followed by a very large excretion of sugar, a larger dose would not have materially increased this output.

Duration of the Glycosuria. The glycosuria after a moderate intraperitoneal dose of adrenalin (say 5–8 c.c. in a dog of 10 kilos) lasts, usually, somewhat less than twenty-four hours. As a rule, the glycosuria is at its height within a few hours after the administration of the adrenalin. The excretion of sugar then declines rapidly, and the urine soon contains only a fraction of 1 per cent. of reducing substance.

Total Quantity of Sugar Excreted. The total amount of sugar excreted under the conditions just mentioned is usually not more than a few grams. The very high percentage sometimes observed soon after the injection of adrenalin might lead one to expect a much larger total excretion than actually occurs. The explanation of this unexpectedly small output of sugar lies in the rapid decline of the glycosuria after the first few hours.

Nature of the Sugar Excreted. No careful study has yet been made of the chemical constitution of the sugar excreted after adrenalin, but there is reason to think that glucose is the chief, if not the sole, carbohydrate constituent of the urine in at least most instances of adrenalin glycosuria. In those cases where the results of titration with Fehling's solution have been compared with the results obtained by fermentation there has been a close agreement. A glucosazon is obtainable without difficulty. The urines examined have shown dextrorotation. The nature of the reducing action of the urine deserves much more careful study, as it is by no means proved that dextrose is the only carbohydrate present in the urine after adrenalin. It should be stated, however, that in no instance has the urine reduced Fehling's solution after fermentation. This renders it most unlikely that glycuronic acid is excreted after the injection of adrenalin solutions.

Sugar Content of the Blood. Numerous observations on the sugar content of the blood before and after the production of adrenalin glycosuria indicate that in well-fed animals there is regularly an increase in the blood sugar. The following observation which was made by Dr. A. N. Richards is in several respects instructive:

A well-nourished dog (7.6 kilos) was fed twelve hours previous to the intraperitoneal injection of 8 c.c. of adrenalin.

Blood.	*Amount.*	*Sugar.*	*Coagulation time.*
Normal	29.0 gm.	0.26 per cent.	4′ 00″
Five minutes after injection	15.0 "	0.36 " "	2 15
Ten minutes after injection	11.5 "	0.40 " "	2 00
Thirty two minutes after injection	10.7 "	0.44 " "	2 20
One hour after injection	11.8 "	0.48 " "	4 10
Five hours after injection	10.8 "	0.31 " "	3 05
Seventeen hours after injection	27.3 "	0.10 " "	3 00

These results, which are typical, speak for themselves and call for little comment. The rapid increase in the blood sugar after injection is striking. Another point of interest is the subnormal content of sugar after the lapse of seventeen hours. The increased rapidity of coagulation noted here has been observed in other instances, but appears to be unconnected with the occurrence of glycosuria.

Dr. Richards has made a careful, detailed study of the behavior of the blood sugar after adrenalin, and his results will soon be published.

The most important observation made upon the blood indicates that during adrenalin glycosuria the sugar content of the hepatic vein is considerably greater than that of the portal vein. Thus, in one instance the portal blood contained 0.1 per cent. of glucose at a time when the hepatic vein had 0.25 per cent.

Influence of the State of Nutrition. In general it may be said that the largest quantities of sugar have been observed in well-nourished dogs that had been recently fed. A marked adrenalin glycosuria may be obtained, however, even in dogs that have to be starved for two or three days. The glycogen content of the liver is undoubtedly a factor of much importance in determining the degree of the glycosuria. Sufficiently careful observations have not yet been made with reference to the influence of this factor, but there is some evidence that after a period of starvation, combined with the administration of phlorizin, the excretion of sugar induced by adrenalin is very small. Thus, in a dog of 20 kilos, after a period of fasting and dosing with phlorizin, 10 c.c. of adrenalin intraperitoneally failed to

cause glycosuria during the first four hours following the injection. During the next twenty hours the urine contained 0.1 per cent. of reducing substance.

On the Apparent Tolerance which Follows Repeated Intraperitoneal Injections of Adrenalin. Observations were made in regard to the effects of repeated injections of adrenalin in four dogs, of which only three were normal, the fourth having had the spleen and one-half the pancreas removed at previous operations.

Injections were usually made every third day with doses gradually increasing. After about one month two of the dogs died in consequence of excessive doses of adrenalin. The remaining animals, including the splenectomized dog, received injections during about two months. It was observed that the usual symptoms of an injection of average size became less pronounced than at the beginning of the experiment, and that the sugar excretion was very much less. In the case of the splenectomized dog, sugar ceased to appear in the urine after the last three injections, although the doses were larger than at the beginning. The appetite was very slight at this period, and there is no doubt that the animals were in a state of partial inanition. To this state of inanition can almost certainly be attributed the failure of sugar to appear after the injection of adrenalin. This is indicated by the fact that in the case of the two dogs just mentioned large quantities of sugar appeared in the urine after small injections of adrenalin made after a two weeks' interval, in which the animals took a liberal amount of food.

Why the symptoms following intraperitoneal injections should grow less pronounced with repeated doses is not yet clear. In regard to these effects a condition of actual tolerance seems to become established. It cannot be said that our experiments prove that no tolerance to the glycosuria-inducing action of adrenalin is established as the result of repeated injections. Such a tolerance is observed in the case of morphin, and apparently depends on an increased oxidizing activity on the part of the cells.

Symptoms of Intraperitoneal Injections. Within a few minutes after the injection of an ordinary dose of adrenalin the animal vomits. After twenty minutes or half an hour a period of intense excitement and restlessness usually sets in and lasts for about an hour. This condition is followed by a period of prostration which is often

pronounced in small dogs. The day following the injection the appetite is usually entirely lost. On the second day the animal begins to eat again, and the signs of prostration are no longer noticeable.

After fatal doses (10–12 c.c. in dogs of 5–8 kilos) the symptoms are similar to those described, but more intense. There is repeated vomiting in many instances, and a bloody diarrhea is usual. The prostration after the period of excitement is profound, and death commonly ensues within twenty-four hours. At autopsy the intestine is found to be the seat of intense congestion or hemorrhage into the mucous and submucous layers, and the greater part of the intestinal tract may be denuded of its epithelium. The pancreas may be the seat of numerous hemorrhages and local necroses, but in other parts the normal appearances may be preserved.

Glycosuria after Local Applications of Adrenalin. At an early period of the research it seemed desirable to determine whether the greater efficacy of the intraperitoneal method in the production of glycosuria was dependent on the better opportunity for the local action of the adrenalin on the pancreas. The pancreas was therefore exposed in a number of normal dogs and adrenalin applied directly to the presenting surface by means of a brush, It was found that marked glycosuria follows the application of small quantities of adrenalin to the pancreas, quantities which, when applied locally to other parts of the body either give rise to no excretion of sugar or to a trivial glycosuria.

As a rule, the local application of adrenalin to the pancreas leads, in a few moments, to a deepening in the color of the gland at the area of contact. Sometimes this local reddening of the surface of the gland is preceded by a marked pallor of the organ, but this appears to be exceptional. The glycosuria usually sets in promptly after an application of 1 c.c. of a 1–1000 solution of adrenalin chlorid. Usually sugar may be detected in the urine within an hour of the application. It has been observed within ten minutes of the painting. Sometimes one or two hours have elapsed before sugar was detected. The minimal dose which is capable of inducing glycosuria has not been determined, but it seems probable that in some small, well-fed dogs, less than 0.5 c.c. of adrenalin (1–1000) would suffice to cause some degree of glycosuria.

The quantity of glucose excreted after applications to the pancreas

varies widely in different instances. The examples just given are typical, but it sometimes happens that, under similar conditions (as regards the weight of the animal, the size of the dose, and the duration of the application), very little sugar is excreted, and in very rare instances no sugar whatever has been detected. On the other hand, we have met with one case in which an ordinary application of adrenalin was followed by a glycosuria of 14 per cent.

By making repeated applications of adrenalin to the pancreas at short intervals, it is possible to induce a very large excretion of sugar. Ultimately, however, there is, as one would expect, a marked falling off in the percentage of sugar and in the volume of urine.

Applications of adrenalin to the pancreas are apt to be most effective when the connective-tissue covering of the gland has been at least partly stripped. But the great differences in the excretion of sugar in different experiments cannot be explained by local conditions. The explanation of these differences will be attempted in another publication.

Examples of glycosuria from local painting of adrenalin are the following:

1. Both surfaces of the pancreas of a dog of 10 kilos were painted with adrenalin (2 c.c. of 1–2000 solution of adrenalin chlorid). Within ten minutes the urine contained more than 5 per cent. of sugar.

2. Dog of 8.4 kilos. Pancreas painted with 1 c.c. adrenalin. Two hours and ten minutes later urine contained 2.8 per cent. sugar.

3. Dog of 5.6 kilos. Pancreas painted with 2 c.c. adrenalin. Three hours after, 0.4 c.c. urine showed strong reducing action.

Control Experiments. It was, of course, of the first importance that control observations should be made in order to determine whether applications of adrenalin to other organs than the pancreas are not followed by glycosuria. The following notes indicate the nature of the results attending such control experiments:

1. Dog, 10 kilos, spleen exposed and painted with 2 c.c. adrenalin (1–1000). During the second fifteen minutes urine shows slight reduction (slight yellowish residue on casserole). Other samples negative.

2. Dog, 11 kilos, fed upon sugar. Two and a half c.c. adrenalin injected directly into the liver substance. Small sample of urine

after three hours contains 0.7 per cent. sugar. Other collections negative.

3. Dog, 10 kilos. Two c.c. adrenalin with 2 c.c. water injected into mesenteric vein. One and three-quarter hours after, urine contained 0.2 per cent. sugar.

4. Dog, 7.5 kilos. Three c.c. adrenalin and 3 c.c. water injected into mesenteric vein. After one hour and ten minutes, sugar, 1.11 per cent.

5. Dog, 9 kilos. Two c.c. adrenalin painted on surface of liver. One and one-half hours after, urine negative.

6. Dog, 8 kilos. Two and one-half c.c. adrenalin with 2.5 c.c. water injected into mesenteric vein. One hour and twenty minutes after injection, urine contained less than 0.5 per cent. sugar.

7. Dog. One c.c. adrenalin applied to surface of pia arachnoid. Urine negative.

These and other observations show plainly that the local application of adrenalin to the pancreas is distinctly more effective in causing glycosuria than is its contact with the liver, spleen, or brain.[1] It should be noted, that although in several of the control experiments much larger quantities of adrenalin were used than in the case of the applications to the pancreas, the percentages of sugar in the urine were small. It seems extremely probable that when adrenalin is infused into a mesenteric vein rather rapidly, as in these experiments, a small amount of the substance reaches the pancreas and acts upon its cells. On the other hand, it is not improbable that in the case of the experiments where adrenalin is painted on the surface of the pancreas a very small quantity of the active material reaches other parts of the body. Since we cannot completely exclude from the circulation the pancreas without producing glycosuria we are unable to say whether the contact of adrenalin with other cells than those of the pancreas is or is not capable in itself of inducing glycosuria. We may, however, feel certain that applications of adrenalin to pancreatic cells are peculiarly effective in the production of glycosuria. The difference between the behavior of pancreatic and other cells in this respect is so pronounced that we are justified in regarding the glycosuria of adrenalin as essentially pancreatic in character.

[1] Applications to the kidney are apt to yield more sugar than similar applications to the liver, intestine, spleen, or brain, but the glycosuria is less marked than after the pancreas has been painted.

The pronounced nature of the glycosuria following intraperitoneal injections appears to be mainly attributable to the readiness with which the adrenalin comes into contact with the pancreas. Experimental injections of colored fluids into the peritoneal cavity give support to this view. Other experiments, which need not be described here, show that when the pancreas is rendered comparatively inaccessible to intravenous and intraperitoneal doses of adrenalin the glycosuria is less than would otherwise be expected.

Other Control Experiments. Control experiments of a different order have been made upon the pancreas to determine whether the necessary manipulation is ever followed by glycosuria. These observations show that the gland may be very roughly handled without causing the appearance of sugar. Bruising, piercing with needles, prolonged stimulation by the galvanic current (kathode 30–50 milliampères), severe burning with the actual cautery, the application of water heated to 60°–70° C., to 80° C., and to 100° C.—all these insults were practised upon the pancreas with wholly negative results so far as glycosuria is concerned.

Nature of the Action of Adrenalin on the Pancreas. The well-known vasoconstrictor action of adrenalin naturally suggested that the explanation of the glycosuria was to be sought in a derangement of the circulation in this gland, probably one induced by narrowing of the arteries. Two observations, however, had been made which appeared opposed to this explanation. In the first place, the local application of adrenalin is followed by an appearance of congestion and not usually by blanching. Second, it was found that after intravenous injections of adrenalin, followed by marked glycosuria, the pancreas in several instances showed, on inspection, no alteration in color which could be interpreted to indicate a change in the calibre of the afferent vessels. Further investigation of the subject showed very clearly that substances may be applied to the pancreas which cause marked congestion but no glycosuria. On the other hand, it was found that a blanching of the gland, as from a 3 per cent. cocain hydrochlorate solution, was not followed by glycosuria, though there is no doubt of the vasoconstrictor action of the drug when thus applied. It was also noted that substances which, like amyl nitrite, exert a vasodilator action are capable (at least under some conditions) of inducing marked glycosuria when applied directly to the gland.

It is therefore impossible to establish any definite relation between glycosuria and the vascularity of the gland or of parts of the gland. It was further observed that there is no relation between elevation of the blood pressure and the glycosuria. Adrenalin was injected into the peritoneal cavity together with sufficient nitroglycerin to keep the systemic pressure much below normal. Yet glycosuria of the usual degree was observed.

While these various experiments do not prove that vascular derangements of the pancreas are of no significance in connection with the production of adrenalin glycosuria, they, nevertheless, point to the conclusion that if such derangements have a part in determining the glycosuria it must be of secondary importance.

Before obtaining a clue to what we believe to be the correct explanation of the nature of adrenalin glycosuria, a number of experiments were made with a view to determining whether the blood drawn from the pancreaticoduodenal vein at the height of adrenalin glycosuria contains any substance capable of inducing glycosuria when injected into the portal system of a normal animal. The observations indicate that even large quantities of blood obtained in this way cause for the most part only a slight glycosuria. As this line of investigation did not appear promising, it was not carried sufficiently far to prove whether the glycosuria noted might not be dependent on the increased sugar content of the injected blood or (which seems improbable) on the presence of unchanged adrenalin in the blood.

The Action of Dilute Solutions of Potassium Cyanid on the Cells of the Pancreas. We are indebted to Professor Jacques Loeb for calling our attention to the important work of Geppert on poisoning by hydrocyanic acid. This suggestion was of much value for our work, as it has given us at least a clue to a better understanding, not merely of adrenalin glycosuria, but of other forms of glycosuria and diabetes. The fact was well known to Claude Bernard that when animals are poisoned with hydrocyanic acid the blood in the veins grows lighter in color and may assume a bright arterial hue. The explanation of this striking phenomena has been given by Geppert in his classical work. This investigator showed that in experimental hydrocyanic poisoning the blood of the veins contains much less carbon dioxid than normal and much more oxygen, the percentage of

oxygen falling only a little below that of the arterial blood. He further showed that the oxygen utilized in the organism is markedly diminished. A very careful scrutiny of all the facts established by Geppert's experiments brought out the conclusion that the disturbance in the gas exchanges of the body are referable to the poisonous action of hydrocyanic acid on the cell protoplasm of the organism. This action is of such a nature that it prevents the cells from taking oxygen from the blood as in health. Hence the blood of the veins assumes an arterial tint.

With a knowledge of Geppert's work in mind, it seemed very desirable to try the effects of hydrocyanic acid on the cells of the pancreas with a view to testing the idea that local disturbances of oxydative function, limited wholly or very largely to this particular group of cells, might give rise to glycosuria. The experiments which have been made bear out the correctness of this idea. A typical experiment is the following:

Dog, about 7.5 kilos, urine normal; 0.5 c.c. of $\frac{N}{1000}$ KCN solution was applied to one surface of pancreas, which became bright red. After thirty minutes the urine showed decided reduction of Fehling's solution. After about one hour urine negative. Then another application of about 2 c.c. of same solution to surface of gland; also 1 c.c. injected slowly into gland. After one hour urine had 2.1 per cent. of glucose, second hour 0.85 per cent. glucose, third hour slight reduction.

Control Experiments. The importance of control experiments is, of course, evident. The following observations are instructive in this connection as checks to the pancreatic applications:

1. Dog, about 17 kilos. Loop of small intestine painted several times with $\frac{N}{1000}$ KCN solution (say from 1 to 2 c.c.), then 2 c.c. of the same solution injected into the subperitoneal layer of the intestine. Urine negative.

2. Dog, about 10 kilos; 3 c.c. $\frac{N}{1000}$ KCN solution injected slowly into mesenteric vein. One hour and ten minutes later urine absolutely negative.

These experiments and others of the same character leave no doubt that the absorption of minute doses of hydrocyanic acid by the cells of the pancreas is followed by a glycosuria of short duration. In the change in the color of the gland we have ocular evidence of the

action of the poison in preventing the cells from taking up oxygen as under physiologic conditions.

The results of experimentation with potassium cyanid made it important to determine the local effects of some members of that large group of substances which have an energetic reducing action. It was thought that the use of such reducing substance might interfere with oxidation within the pancreatic cells, and thus give results comparable with those obtained with potassium cyanid.

Effect of the Application of Reducing Substances to Pancreas. Only the briefest references can here be given to the action of the various reducing substances which were employed.

Sulphurous Acid (SO_2). An application of 0.5 c.c. of a saturated aqueous solution of SO_2 was made to the pancreas of a dog of 7 kilos. The gland whitened as from coagulation of proteids. Urine before operation negative; forty-five minutes later about 2 per cent. sugar.

Ammonium Sulphid $(NH_4)_2S$. The pancreas of a dog of 5.5 kilos was painted with 0.5 c.c. of an ammonium sulphid solution made by passing sulphuretted hydrogen through standard ammonium hydroxid solution of 0.96 sp. gr. Urine one hour after showed slight reduction, three hours after about 1 per cent. of reducing substance. In a second experiment of the same kind the glycosuria was less marked.

Sulphuretted Hydrogen. A small current of sulphuretted hydrogen was allowed to flow against the surface of the pancreas for fifteen minutes. The dog weighed 10 kilos. Two hours later the urine showed slight reduction.

Illuminating Gas. A stream of illuminating gas was allowed to flow against the surface of the pancreas of a dog of 19 kilos for one hour. Urine after this contained 1.7 per cent. of reducing substance.

Carbon Monoxid (CO). Twenty liters of pure carbon monoxid warmed to the body temperature were allowed to flow for one hour against the pancreas of a dog of 7.8 kilos. The urine after this contained a small quantity of reducing substance.

Benzyl Alcohol ($C_6H_5CH_2OH$). Two c.c. of benzyl alcohol were applied to the pancreas of a dog of 12 kilos. Three hours later the urine contained 3.57 per cent. of sugar. The color of the gland deepened, but there were no indications of coagulation.

Pyrogallol and Allied Phenols. The well-known affinity of pyrogallol (1-2-4 trihydroxyphenol) for oxygen suggested the use of this substance, which was employed in aqueous solution without addition of alkali. The following are typical results of trials made with this substance:

1. Dog, 6.4 kilos. The pancreas was painted with 1 c.c. of pyrogallol in 1–8 dilution. Three and three-quarter hours after 30 c.c. of urine contained 8 per cent. sugar.

2. Dog, 6 kilos. Two c.c. of pyrogallol (1–5 dilution) were painted on the pancreas. Two hours after urine contained $\frac{2}{3}$ per cent. sugar. Phloroglucin (symmetrical trihydroxyphenol), hydroquinon, and pyrocatechin gave much slighter glycosurias than pyrogallol, but the observations are not sufficiently numerous to be conclusive.

Sodium Salicylate. This salt has proved capable of inducing a glycosuria of very high percentage when used in considerable concentration. Details of experiments with this substance will be reported elsewhere.

Pyridin, Piperidin, and Quinolin. Experiments made with pyridin and piperidin are of a special interest, because, as shown by Abel, a conium-like substance is present in the active blood pressure raising constituent of the suprarenal gland, and this alkaloid is known to contain a pyridin base. Pyridin reduces potassium permanganate in alkaline solution, but not in neutral solution, and one would not predict for it a marked action in the production of glycosuria. In three dogs in which a 1–10 aqueous solution of pyridin was painted on the pancreas there followed only slight glycosuria. Piperidin (hexahydropyridin) has a chemical constitution which indicates a much greater reducing activity than that of pyridin. In six dogs in which aqueous solutions of piperidin (1–10 or weaker) were brought into direct contact with the pancreas large percentages of sugar were found in the urine—in one instance 11.7 per cent. It should be stated, however, that in another dog piperidin failed to cause the appearance of sugar. Here the failure of the sugar to appear did not appear to be connected with the quantity of piperidin used, for many times the usual dose was applied in this instance without leading to glycosuria. The explanation of these exceptional cases is not yet clear. In two instances where the sugar of the blood has been determined the glycosuria after piperidin has apparently not been associated

with an increase of blood sugar, which suggests that there may be a renal element in these glycosurias. Quinolin appears to stand midway between pyridin and piperidin in its ability to produce glycosuria.[1]

The Relation between Adrenalin Glycosuria and the Reducing Action of Adrenalin Chlorid. The observations to which reference has been made rendered it not improbable that the action of adrenalin in causing glycosuria is connected with its reducing activity. It was very easy to demonstrate that any oxidation of adrenalin chlorid outside the body which deprives it of its reducing power and of the characteristic Vulpian reaction with ferric chlorid also destroys its action in raising the blood pressure and in causing glycosuria. Numerous experiments with oxidizing agents, including potassium permanganate and chlorin gas, showed that adrenalin thus deprived of reducing action could be injected intraperitoneally in large amounts without producing any glycosuria, or, indeed, any symptom whatever. The chemical nature of the substance or substances that result from the oxidation of adrenalin chlorid is not yet known. Violent shaking with considerable volumes of neutral oxygen for periods of one or two hours caused a reddening of the adrenalin solution, but failed to deprive it of the ferric chlorid reaction or of its ability to induce glycosuria.

Control Experiments with Substances Which do Not Reduce. The importance of control observations makes it desirable to give brief abstracts of some individual experiments which were made as checks to the studies with reducing substances.

1. Dog, 7 kilos, Two c.c of a 13.5 per cent. ferric chlorid solution painted on pancreas, which whitened from coagulation. Urine, one hour and three hours later, negative.

2. Dog, 9 kilos. A 5 per cent. sodium chlorid solution (of about body temperature) was allowed to flow on surface of pancreas for twenty (?) minutes; 280 c.c. were used. One hour later 30 c.c. urine gave less than 0.1 per cent. of reducing substance on long boiling. Five c.c of this urine with 10 c.c. Fehling's solution caused no reduction. Five hours later, urine doubtful, possibly slight reduction.

[1] Other substances which were tried, a quinin and an atropin, both of which in moderate concentration, were followed by glycosuria. Experiments were also tried with diphtheria toxin and tetanus toxin. The former induced glycosuria when applied to the pancreas; the latter did not. The details of these experiments, together with others made with rattlesnake venom and with various alkaloids, will be given in another paper.

3. Dog, 9 kilos. Ten per cent. solution of sodium hydroxid painted on pancreas; 1 c.c. being used. One hour later, urine gives slight but undoubted reduction. Two and five-eighths hours after, slight reduction. Four hours after, no reduction. Five hours after, no reduction.

4. Dog, 8 kilos. One c.c. 10 per cent. hydrochloric acid painted on pancreas. One, three, and five hours later urine showed no reduction. A similar experiment gave a negative result.

5. Dog, 7.5 kilos. Pancreas painted with 3 c.c. bromin water. After one hour very slight reduction (trace). Later collections negative.

6. Dog, 8 kilos. Pancreas painted with 3.6 c.c. chlorin water. Urine, several collections, negative. Second collection (after two and three-quarters hours), slight suspicion of reduction, probably negative.

7. Dog, 9 kilos. Pancreas painted with 2 c.c. fresh hydrogen peroxid (Marchand's).

8. Dog, 19 kilos. Pancreas painted with 2 per cent. solution of chromic acid, 2 c.c. used. No symptoms. Urine negative.

9. Dog, 7.4 kilos. Two c.c. of a saturated solution of $KClO_3$ were painted on the pancreas. Two and a half hours after, urine negative.

10. Dog, 9 kg. Two c.c. of 2 per cent. HNO_3 solution were painted on the pancreas. Two hours after, urine negative.

This group of control experiments shows quite clearly that applications which are by no means indifferent in character may be made to the pancreas without causing glycosuria. Some of these substances have neither reducing nor oxidizing qualities, but are, nevertheless, distinctly injurious. Thus, ferric chlorid and hydrochloric acid coagulate the protoplasm of the cells with which they come in contact, and there can be no doubt that a 5 per cent. sodium chlorid solution disturbs the normal osmotic conditions within the pancreatic cells. Other substances used possess a strong oxidizing action, but failed to cause the appearance of sugar. The only oxidizing substance hitherto used which has given rise to decided glycosuria is picric acid employed as a saturated aqueous solution. Nitrobenzine and other nitrocompounds have not yet been tried.

Relation between Experimental Pancreatic Glycosuria and Interference with Normal Oxidations of Pancreatic Cells. The experiments heretofore made indicate plainly that a close relationship exists

between the reducing power of a substance and the capacity of this substance to induce glycosuria when applied directly to the pancreas. There are, indeed, substances which possess active reducing power, but which have yielded only slight degrees of glycosuria. On the other hand, there is at least one poison, hydrocyanic acid, which is capable of bringing on glycosuria, although it exerts little reducing action. As yet, picric acid is the only oxidizing agent which has been found to cause glycosuria when applied to the pancreas, but it is very probable that there are other oxidizing substances with a similar action. Our present experience indicates that substances which have a strong reducing action are very much more likely to induce glycosuria than those which lack this power, although it also indicates that the ability to produce glycosuria is not always proportional to the reducing activity as measured *in vitro*. Thus a solution of adrenalin chlorid of a given reducing power, will cause much more glycosuria than a solution of hydroquinon of the same reducing activity. Nevertheless, it appears that among substances of allied chemical constitution the ability to induce the appearance of sugar in the urine may be, at least, roughly proportional to the reducing activity. We see this among substances of the pyridin and phenol groups.

It is not yet clear what interpretation should be put on the association of the power to reduce and the power to induce glycosuria. The striking case of hydrocyanic acid, which acts by poisoning the cell so that it no longer takes up oxygen normally, suggests that the various reducing substances act by removing oxygen from the pancreatic cells. The quantity of oxygen thus removed can be calculated. It is so small in the case of a powerful glycosuria-inducing agent, like adrenalin, that we must hesitate to ascribe the appearance of sugar to the mere removal of this small amount of oxygen from the cells. Moreover, we know that there are substances with marked reducing action (sodium thiosulphate), which induce only slight glycosuria and are acquainted with at least one poison (hydrocyanic acid) which induces glycosuria, without having any reducing action.[1] We are, therefore, inclined to attribute the glycosurias we have noted not necessarily to the reducing action of the substances concerned, but to some toxic

[1] Sodium fluorid appears to be another substance belonging to this class.

action on the cells. This action is, however, closely connected with the power of reduction. It is possible that in some instances (as in the case of carbon monoxid poisoning) the quantity of oxygen removed from the cells is sufficient to account for the disturbance in the function of the gland.

Of the intimate nature of this functional disturbance we know nothing as yet. The instructive case of potassium cyanid suggests that in many cases the cells are poisoned in some way which interferes with their oxidative activities.

The discussion of hypotheses relating to this fundamental question will not be undertaken here.

On Glycosurias following Applications to One Portion of the Pancreas. Early in the course of the study of adrenalin glycosuria it was observed that the reddening of the gland which commonly follows immediately upon an application of adrenalin is localized to the area of contact, and superficial. This observation raised the question whether the action of the adrenalin is actually limited to the parts which show an alteration in color, or whether there is a diffusion of the substance through the gland, such as must occur when an intravenous infusion of adrenalin is followed by glycosuria. In order to form an opinion on this important point a special form of experiment was devised. The pancreas was cut through at right angles to its axis, and the incision was carried quite through the adjoining duodenum. The bleeding vessels having been clamped or tied, an application of adrenalin chlorid was made to one portion of the pancreas, special care being taken that none of the substance should come into contact with the unpainted part of the gland. This form of experiment was used not merely with adrenalin but with potassium cyanid and pyrogallol. The following notes indicate the nature of the results:

1. Dog, 4.5 kilos. Pancreas divided into two portions, a splenic, one-third, and a cephalic, two-thirds. The splenic one-third was painted with 1–1.25 c.c. adrenalin chlorid (1–500). One and one-half hours after, 13.5 c.c. urine contained 10 per cent. of sugar.

2. Dog, 7.4 kilos. Pancreas divided into a cephalic one-fifth and a splenic four-fifths. The cephalic fifth was painted with 1 c.c. adrenalin chlorid (1–500). One and one-half hours after, 8.5 c.c. of urine contained 3–4 per cent. of sugar.

3. Dog, 9.5 kilos. Pancreas cut into two nearly equal halves. Splenic half painted with 1 c.c. $\frac{N}{1000}$ KCN solution, also 1 c.c. of same solution slowly injected into this part of the gland. Thirty minutes after injection urine contained 6 per cent. of sugar.

4. Dog, 7.4 kilos. Pancreas cut into a cephalic three-fifths and a caudal two-fifths. Splenic two-fifths painted with 1.5 c.c. $\frac{N}{1000}$ KCN solution. Two hours later 5 c.c. urine contained about 1.5 per cent. sugar.

5. Dog, 10.1 kilos. Pancreas divided into a caudal two-thirds and a cephalic one-third. Cephalic end painted with 1 c.c. pyrogallol solution (1–5) (not rendered alkaline). One and three-quarter hours after 4 c.c. urine show slight reduction. Two c.c. of urine with 10 c.c. Fehling gave yellow deposit on casserole.

What interpretation are we to put on these experimental results? So far as the pancreas is concerned, the glycosuria which follows the local application to the portion of the gland must either depend on the absorption of the toxic substance by this portion of the gland alone, or upon absorption by the unpainted as well as the painted portion. In the former case we must suppose that the substances applied to the gland do not enter the blood in sufficient amount to exert any effect upon the remaining piece of the pancreas. In the latter case we must suppose that these substances do enter the blood in an amount sufficient to act on the detached piece of the gland. If the latter view is correct we are dealing with a phenomenon comparable to the elimination of functions that occur when much the greater part or all of the pancreas of a dog is extirpated. But if this view is not correct, and the glycosuria arises from an effect limited to one part of the pancreas, we are dealing with a phenomenon very different from the glycosuria of total extirpation. This conclusion is forced on us by the fact that a glycosuria may follow an application to much less than one-half the pancreas; whereas, as is well-known, the extirpation of one-half the pancreas from the dog is only exceptionally followed by sugar in the urine. Owing to experimental difficulties, which need not here be considered, it has not been possible to decide this important point definitely.

Control experiments already referred to, together with others that have not been mentioned, indicate that doses of potassium cyanid from four to six times greater than those (or even very much larger)

required to induce glycosuria when applied to the pancreas, fail, when infused into the circulation, to cause the appearance of sugar. This fact renders it extremely improbable, in the case of hydrocyanic acid at least, that any of the poison painted on one portion of the severed pancreas reaches the remaining portion of the gland.

Numerous observations have also been made with adrenalin. Relatively small infusions of adrenalin into the circulation give rise to a slight degree of glycosuria, doubtless of pancreatic origin. Hence, it is less easy than in the case of applications of potassium cyanid to absolutely exclude some action of the adrenalin upon the portion of the pancreas which has not been painted. Nevertheless, we are prepared to state that it is most unlikely that the glycosurias we have observed after painting one end of the pancreas are in any significant degree dependent on the implication of the entire pancreas.

This view of the action of adrenalin on the pancreas carries with it important physiologic corollaries. Since glycosuria is occasioned by applications confined to one portion of the pancreas (one-half or less) this disturbance must be something quite different from the glycosuria which follows extirpation of the entire pancreas or its greater portion. The transient nature of the glycosuria is another feature of difference from the extirpation diabetes, the cells of the pancreas being capable of complete recovery. It is, of course, possible that the glycosuria after local applications of potassium cyanid or adrenalin chlorid, depends on the elimination of a function of the cells of a particular part of the pancreas. It seems, on the whole, more probable that it depends ultimately on an over-stimulation of physiologic activity of certain cells of the gland. There is some evidence that the hyperglycemia after adrenalin is hepatic in origin, in the sense of being due to an excessively rapid conversion of glycogen into dextrose and that the pancreas is in some way concerned with the regulation of the change of glycogen into sugar. Whether the regulation of this hepatic function occurs through the mediation of the sympathetic nervous system, or whether it depends on the more direct influence of substances reaching the liver from the pancreas, is entirely unknown.

The idea that the glycosuria from adrenalin or potassium cyanid poisoning depends on the stimulation rather than on the complete elimination of a function of the pancreas does not appear inconsistent

with the view that these substances act by interference with the oxidations in the pancreatic cells. It is conceivable that these poisons inhibit the action of a pancreatic enzyme, which normally checks the action of substances capable of favoring the conversion of hepatic glycogen into sugar. It is also possible that these poisons stimulate the nerve endings in the pancreas, by interference with oxidation, in such a way as to bring about an increased flow of blood through the liver through the mediation of the sympathetic ganglia. The discussion of these possibilities, however, only serves to emphasize our ignorance of the real processes concerned with the production of the glycosurias we have described. Extensive experimentation is essential to bring us to the light.

Relations between Human Glycosuria and the Experimental Glycosurias from the Action of Reducing Substances and other Poisons. It is proper to refer briefly to the bearing of this research upon the interpretation of the phenomena of human glycosuria and diabetes. Our experiments show that a large variety of substances applied to the pancreas in the dog are capable of inducing glycosuria, probably by interfering in some way with the oxidations carried on by the pancreatic cells. The very intimate connection of the pancreas with these glycosurias leads one to ask whether there are not many examples of human glycosuria of similar origin. The glycosuria following conditions of asphyxia, as, for instance, after epileptiform seizures, can probably be referred to interference with the oxidations in the pancreas. The glycosurias noted after poisoning with carbon monoxid can, we believe, almost surely be explained by the effects of this gas on the pancreas. In the case of the ordinary chronic forms of human diabetes, with or without marked lesions in the pancreas, we are not yet in a position to speak positively, but our research suggests an explanation which may apply to many instances of this sort. It has long been known to physiologists that easily oxidizable reducing substances are constantly being produced in the organism, and that the combustion of these substances is one of the fundamental activities of living protoplasm. We know that at least one gland,[1] the supra-

[1] The following demonstration of the reducing activity of this gland is very striking. If a dog be injected with a preparation of alizarine blue, the blue particles will be found in those organs which have little or no action in reducing the pigment to a colorless substance. But in cells which reduce strongly (muscles, lungs, suprarenal glands) the blue color rapidly disappears and the suprarenal gland appears in striking contrast.

renal, produces a reducing substance which is of great importance for the maintenance of the general vascular tone, and it is likely that there are other reducing substances formed by other kinds of cells, dextrin itself being for the moment left out of account. The blood containing these bodies streams through all parts of the animal mechanism, including the pancreas. If, now, we imagine a disturbance in the normal balance between the oxidizing activities of the pancreatic cells and the production of reducing substances in other parts of the organism, it is easy to understand how a functional inadequacy of the pancreas might arise which would interfere (through an unknown mechanism) with the normal combustion of sugar and its appearance in the urine. If this conception be correct the presence or absence of glycosuria in any organism may depend on the relation between two variable factors, production of toxic-reducing substances on the one hand, and oxidative pancreatic activity on the other. The effect of an excessive production of reducing substances (as from diseases of the suprarenal gland) would be equivalent to a reduction in the efficiency of the pancreatic cells. In most cases of diabetes both factors may coexist. Such a conception of the nature of diabetes helps to explain those instances where the pancreatic lesions are slight in degree.

This idea is put out as a suggestion, not as a fact. A large amount of very careful experimental work, involving a good technic, is necessary to determine whether it has any substantial foundation. The establishment of the fact that the blood of some diabetic patients contains an excess of reducing substances other than dextrose would give substantial support to the conception here advanced.

Histologic Alterations in the Pancreas and Experimental Pancreatic Glycosuria. Experiments to which no reference has yet been made indicate that histologic alterations in the pancreas are not a necessary condition of adrenalin glycosuria. Bits of pancreas removed before the production of such glycosurias were compared with bits removed at the height of the sugar excretion. Tissue fixed in Ohlmacher's fluid and in formalin, and stained by the ordinary methods,[1] failed to show recognizable alterations.

After fatal doses of adrenalin by peritoneum the pancreas may be the seat of focal necroses and the islands of Langerhans may be the

[1] Dr. E. K. Dunham and Dr. Alice C. Brown were so kind as to make these preparations.

seat of destructive changes, but we attach no significance to these lesions in their relation to glycosuria.

It is instructive to note that glycosuria may follow the application of various substances to that portion of the pancreas which contains relatively few of the cell clusters of Langerhans. It is impossible to state whether a more marked glycosuria follows applications to the tail of the organ (rich in islands of Langerhans) than to the head. Perhaps a large number of experiments made under conditions nearly alike would throw some light on this point, but a small number of observations could not decide it. The observations which have been made up to the present time do not indicate any distinct difference in the results from painting the tail and painting the descending cephalic part, which, in the dog, is most free from Langerhans' islands. Thirteen experiments have been made. The head was painted first in some instances. In other cases the tail was painted first. Many of the dogs used for these experiments had been under observation only a short time and were probably not well fed. It is possible that more marked differences in the glycosuria following applications to the head or tail will be noted when we take the precaution of feeding the animals on carbohydrates previous to the operation.

The Physiologic Significance of the Experimental Method Employed in this Research. It has been shown that various substances applied directly to the pancreas are capable of acting on the cells of this gland in such a way as to induce glycosuria. Evidence has been brought out which makes it in a high degree probable that these substances, so varied in chemical composition, act through their interference with the oxidations normally carried on by the protoplasm of the pancreatic cells, though in a manner as yet unknown to us. The fact that so many substances which interfere with oxidative processes are capable of inducing glycosuria, deprives adrenalin glycosuria of some of the special significance which attached to it before it was discovered that so many allied varieties of pancreatic glycosuria are readily induced.

The case of adrenalin glycosuria will always be invested with that special interest which comes from circumstances that adrenalin chlorid is representative of an important internal secretion. It is, however, an essential gain to physiology that we now recognize the glycosuria from suprarenal extracts to be a particular example of glycosuria from

reducing substances rather than a wholly isolated and unrelated form of disturbed carbohydrate metabolism.

But just as we must look upon adrenalin glycosuria as one of a large number of forms of pancreatic glycosuria from some derangement in the oxidative functions of a particular gland, so must we look upon all pancreatic glycosurias from disorders of oxidation as a particular case of disturbed oxidation. By means of local applications of substances like potassium cyanid, adrenalin, and piperidin to other types of animal cells, we may reasonably expect to interfere profoundly with the oxidations there carried on. Thus it seems likely that we possess a method which will teach us much of importance about the metabolic activities of the kidneys, the muscles, and perhaps the nervous system. Interference with the activities of the pancreatic cells gives us a striking signal, glycosuria, but there is every reason to think that other groups of cells may be thrown out of action with equal precision, if not with equally obtrusive metabolic effects. The kidney of one side can be thrown out of function, so far as oxidations are concerned, without gross mechanical insults. One would expect that while the "vital" functions are thus placed in abeyance the processes of diffusion and filtration would be little disturbed. By means of such a method it seems not unreasonable to hope for new light as to the origin of uric acid, glycuronic acid, hippuric acid, etc.

Experiments which we have made suggest that there are other substances than phlorizin which, acting on the cells of the kidney, lead to glycosuria. It is not impossible that adrenalin, while acting chiefly on the pancreas, when intravenously infused acts also on the kidney. On this and allied topics a further report will be made.

At present it is desired that our research be regarded as an introduction to a better knowledge of the all-important subject of oxidations and reductions in the organism, as well as a contribution to the pathology of adrenalin glycosuria.

NOTE A.—It is desirable to make reference to certain conditions of the experiments which constitute the basis of the research. The dogs used were well-nourished and were operated upon within twenty-four hours after a meal of raw beef, which, with few exceptions, was the habitual diet. Previous to each experiment the urine was care-

fully removed by catheter and examined for sugar, the bladder being thoroughly emptied. In all cutting operations the animals were fully anesthetized with ether. They were taken from the holder promptly after recovering from the effects of ether in order to have them under comfortable and natural conditions. Morphin and other substances which cause the appearance of reducing substances in the urine were never employed as narcotics.

NOTE B.—It will naturally occur to the reader that the substances employed in the experiments may have passed into the urine unchanged, thus accounting for some reducing action on the part of the urine. In the case of adrenalin and piperidin the reducing power of small amounts actually used is so small that it would entirely fail to account for the sugar which was detected, even if the entire quantity used came through unchanged. In the case of carbon monoxid the question of passage into the urine does not arise. Sodium fluorid has no reducing action outside the body, and that of potassium cyanid is extremely slight. After pyrogallol a fermentable sugar appears in the urine.

For these and other reasons (especially the results of the control experiments) there is no reason to ascribe the glycosurias noted in our experiments to the excretion of the reducing substances used.

DISCUSSION.

DR. MELTZER: At the outset I wish to express my appreciation of the valuable statements made by Dr. Herter in the paper we just heard. The facts observed by Dr. Herter amount indeed to discoveries. He found, in the first place, that intraperitoneal injections of adrenalin produce much larger quantities of sugar in the urine than the subcutaneous injections of suprarenal extract as it was employed by Blum and others. Then he made the remarkable observation that painting of the pancreas with adrenalin causes also the appearance of large quantities of sugar in the urine. This last observation Dr. Herter connects with the observations of v. Mering and Minkowski, according to which the removal of the pancreas is followed by the appearance of sugar in the urine. Dr. Herter interprets his own observations by assuming that the painting with adrenalin deprives the cells of

the pancreas of their oxygen—that is, the painting causes the elimination of the function of the pancreas. It seems to me, however, that there is quite a striking difference between the effects of the removal of the pancreas and those of the painting of this gland with adrenalin. If four-fifths of the pancreas is removed and only one-fifth left, or if the entire pancreas is removed and one-fifth again replaced in the peritoneal cavity, no appearance of sugar follows. With the painting of the pancreas, however, it is different. If only one-fifth is painted it is sufficient to produce glycosuria. If the painting would mean the elimination of the function of the pancreas, then even the painting of four-fifths of it should not cause glycosuria. One gets rather the impression that the effect of painting is not that of the elimination of a function, but rather of the stimulation of something; and here I am reminded of the experiments of the Cavazzani brothers, that stimulation of the celiac ganglion causes glycosuria. Could it not be that some of the adrenalin while painting the pancreas escaped also to the neighboring ganglion, and thus caused glycosuria?

There is another point I wish to touch upon. It is regarding the capsule of the pancreas. At my suggestion Dr. Emerson, Demonstrator of Physiology in the College of Physicians and Surgeons of New York, is now studying the significance of the capsule to its organ. I have observed years ago that when an organ with an intact capsule is bathed with any kind of fluid, the fluid does not become absorbed into the organ. I have gradually formed the conception that each organ is an individual for itself, and all organs of the animal body are connected with one another only by means of nerves, blood, and lymph vessels, and that it is the capsule which makes each organ an independent individual body. Dr. Emerson's studies extend for the present on the capsules of the kidney, spleen, pancreas, and submaxillary gland. On the kidney it was observed that when it was bathed in either sodium salicylate, potassium iodid, or potassium ferrocyanid, and care was taken that the fluid did not come in contact with any part of the surrounding body, none of the fluid appeared in the urine, even if the kidney remained in it for hours. But if the capsule was incised and removed only from a small area of the kidney, the mentioned substances could be discovered in the urine five minutes after the kidney came in contact with them. This shows that the capsule is fully capable of protecting the kidney against the invasion of any substance from outside. Now, it strikes me with regard to the experiments of Dr. Herter, how it could be possible that the fluid painted in the capsule could reach the cells of this organ. Does not this again support the view that painting stimulates something outside the pancreas?

One more point I wish to discuss. Blum and other investigators who have experimented with injections of suprarenal extract before Dr. Herter have obtained better results by subcutaneous injection than did Dr. Herter. But all the other observers—Blum, Zülzer, Crofton—have employed in their experiments aqueous solutions of suprarenal extract, while Herter employed

exclusively adrenalin chlorid prepared by Dr. Lakamine. Now, here is a very important difference between those two preparations. The aqueous solutions were not subjected to the influence of higher temperatures. Blum, for instance, who wished to have his product sterile, has employed for this purpose either fractional sterilization—that is, heating his solution to 60° C. for one hour on three consecutive days, or he filtered his solutions; and he states that the solutions which were subjected to fractional sterilization yielded a good deal less sugar than the solutions made sterile by filtration. Now, Lakamine prepares the adrenalin by subjecting the fluid to a temperature of 60° C. for many consecutive hours, and then for one hour or longer to a temperature of over 90° C. It would seem to me that the contradiction between the results of Dr. Herter and of the other investigators could be explained by the assumption that the suprarenal contains two substances—one which is thermostable and another which is thermolabile. The thermolabile substance becomes destroyed by prolonged heating, already at 60° C, while the thermostable substance can stand a heat of 90° C. and more. Blum and Crofton and others who employed an aqueous extract which was not subjected to higher temperatures have obtained results from the thermolabile substance as well as from the thermostable one; while Herter, who employed exclusively Lakamine's adrenalin chlorid, had in his hands only the thermostable substance, which apparently has no influence when used subcutaneously, but which is very active when introduced into the peritoneal cavity, perhaps indeed on account of its great reducing power. My remarks are not made in a spirit of contradicting any of the statements of Dr. Herter, but are suggestions thrown out for the purpose of stimulating further the study of this highly interesting subject.

DR. CUSHING: I would like to ask Dr. Herter something about his technic. I have found it exceedingly difficult to do any vivisection with any degree of certainty, because most any operation was liable of itself to induce glycosuria; particularly is this so in rabbits. In dogs I find that the anesthetic is very liable to produce the condition. The curare diabetes has been shown to be purely one of asphyxia, a lessened oxidation being shown to produce it, and Dr. Herter's work is important in reducing this oxidation glycosuria to a condition produced in the pancreas.

DR. HERTER: In reply to the last speaker, I may say that the suggestion made does not apply in the slightest degree to the work I have reported, because I have taken the very greatest precaution on all these points. I did not use morphin, chloroform, or curare in any of these experiments. I have used only ether, and after you have used this for hours on dogs and examined the urine you get only a slight trace of sugar or none whatever—not such percentages, as I have shown, ranging from 4 to 12 per cent. I feel sure the anesthetic does not enter into the question in my work.

In regard to Dr. Meltzer's remarks I feel differently. I feel that in so far as

the explanation of these phenomena is concerned we must wait. Dr. Meltzer has thrown out some suggestions [the speaker turned to address Dr. Meltzer and could not be heard at the desk] in regard to the possible part played by the nervous system which are well worth considering. In some way the application of adrenalin and other substances to the pancreas causes the liberation of an excessive quantity of carbohydrates in the liver. Whether this depends on a disturbance of normal enzyme action or on nervous influences is by no means clear. It is possible that substances like adrenalin act upon nerve-endings in the cells of the pancreas and, through the agency of the sympathetic system, upon the liver.

THE SYMPTOMS AND TREATMENT OF HEPATIC CIRRHOSIS IN THE LIGHT OF SEVENTY-EIGHT AUTOPSIES.

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WITH

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OF BOSTON.

The cases which form the basis of this paper comprise practically all in which a histologic diagnosis of hepatic cirrhosis has been made at the Boston City Hospital since January 1, 1896, and at the Massachusetts since October 19th of the same year. Some have been omitted in which the connective-tissue formation was undoubtedly due to the passive congestion of cardiac disease, as well as a few in which it was local and associated with evidence of active syphilis. While other points have been incidentally considered, the special object of this analysis was to determine how far the most marked symptoms which have been attributed to hepatic cirrhosis were due to the anatomic condition of the liver *per se*, and how far they were dependent on associated changes in other organs. As a corollary to this, the attempt has been made to determine in what class of cases, if any, surgical interference, whose only object is to overcome the portal obstruction, was most likely to prove successful. As they include all grades of cirrhosis, from its earliest to its most developed forms, these 78 cases have been grouped for analysis into four classes, according to the amount of connective-tissue formation, as shown by the microscope, Class I. having the least. Although not free from criticism, this seems a fairer means of estimating the extent of the process than to rely on the size of the liver, since large and small livers were found indiscriminately distributed among our four classes

irrespective of the extent of the fibrotic changes. We are indebted to Dr. F. B. Mallory for his careful examination of each case with this end in view, and to the staff of the Massachusetts General Hospital for the privilege of using their material.

Etiologically, alcohol was the most important factor, for only 9 denied its abuse to whom the question was specifically put, and in several of these there was reason to doubt the accuracy of their statement. Malaria was recorded in the history of 10 patients, and syphilis was either acknowledged or undoubted evidence of its presence was found at autopsy in 9. Seven of the former and 5 of the latter were also alcoholic. Syphilis appeared as the only cause mentioned in 4, and malaria in 3, but no characteristic malarial lesions were present in any. Gallstones were found in 8 cases, in 3 of which they were in the common duct. In the others there was no reason to consider that they had offered more than temporary obstruction to the passage of bile. Omitting the cases from consideration of which the records were silent as to the use of alcohol, either from the moribund state of the patient at entrance or from inadvertence, there remain but 2 in which one or more of the conditions just mentioned did not appear. In these no etiologic factors could be found.

Fifty-two of the patients were males, 26 females. The youngest was sixteen and the oldest sixty-eight years of age.

The accompanying table shows the large number of processes of a chronic degenerative nature which were present in other organs. They were as frequent in the early as in the more advanced cases, and in the former had often made the greater progress. Numerically the most important were arteriosclerosis and renal disease. The former was noted 49 times; often, however, confined to a small patch in the aorta. Chronic nephritis, either diffuse or interstitial, occurred in 23 cases (29.4 per cent.). This proportion is but slightly larger than that given by the combined statistics of Cheadle, Rolleston,[1] and Foxwell,[2] which showed that the kidneys were affected in 114 of 488 cases (25.4 per cent.). Some chronic affection of the myocardium other than simple hypertrophy, or of the valves, was found 37 times (47 per cent.) against 66 per cent. found by Cheadle[3] in 36 cases.

[1] Diseases of the Liver. Encyclopedia Medica, 1900, vol. vi.
[2] Birmingham Medical Review, March, 1896, vol. xxxix. p. 129, April, p. 215.
[3] Lancet, London, 1900, vol. i. pp. 903, 985, 1035.

Chronic Changes in Other Organs.	*Class I.*	*Class II.*	*Class III.*	*Class IV.*	*Total.*
Number of cases used	4	16	35	23	78
Arteriosclerosis	3	12	21	13	49
Aortic aneurism	...	...	...	1	1
Heart, simple hypertrophy	1	2	2	3	8
" hypertrophy and dilatation	1	...	2	3	6
" fatty degeneration	...	2	11	6	19
" myocarditis	...	...	2	...	2
" chronic endocarditis	...	5	5	3	13
" chronic pericarditis, general	...	1	1	1	3
Lungs, tuberculosis, healed	...	3	2	3	8
" tuberculosis, active	...	2	2	1	5
Tuberculosis elsewhere	...	1	1	...	2
Emphysema and bronchitis	...	2	1	1	4
Bronchiectasis	...	...	2	...	2
Pleurisy, adhesive	2	8	19	11	40
Kidneys, passive congestion	...	1	1	1	3
" chronic nephritis	2	4	11	6	23
" fatty degeneration	...	3	6	6	15
" amyloid	...	1	1	...	2
" hydronephrosis	...	1	...	...	1
Peritonitis, general	..	4	7	4	15
Perihepatitis, general	1	5	3	4	13
" local	3	1	9	5	18
Perisplenitis	2	3	11	7	23
Pancreatitis	...	...	1	1	2
Gallstone	...	2	4	2	8
Gastro-intestinal tract, passive congestion	1	4	10	4	19
Gastroduodenal catarrh	...	...	...	1	1
Gastric ulcer	...	...	...	1	1
Dilated stomach	...	1	...	...	1
" colon	...	...	1	1	2
" intestines	...	...	1	1	2
Brain atrophy	...	1	...	1	2
" lepto- and pachymeningitis	...	2	1	...	3
Orchitis	1	...	2	...	3
Cancer	...	...	2	...	2
Dilated veins	1	4	9	15	29

A diagnosis of hepatic cirrhosis is, therefore, often no more complete than one of cardiac disease in the presence of a general arteriosclerosis, although emphasizing the most striking feature, since it ignores the fact that the complications may result from the same causes producing the hepatic condition, and be, in part at least, responsible for some of the symptoms. In 17 instances, however, they were either absent or were so slight as to be of no importance. Three belonged to Class II., 4 in Class III., and 10 in Class IV. They are of interest in showing that a high degree of fibrosis may be found in the liver without marked interference with its functions, and without producing characteristic symptoms. Eight of these cases, 4 of which were in Class IV., died of incidental causes not associated with hepatic cirrhosis, which the patient had had no reason to suspect.

Splenic enlargement was fairly constant, being present in 65 of the cases, but its increased size in 27 was probably due, in part at least, to an acute process. Chronic passive congestion was undoubtedly an important factor in producing the enlargement of many of the other 38, but it would not account for the increase in size not infrequently found where the hepatic process was but slight, nor could a close relation between the size of the spleen and the presence of the ascites be detected. The largest spleens were found in Classes III. and IV., yet some of the biggest were present in cases without ascites, and some of normal size were found with marked ascites. It, therefore, appears that the size of the spleen may depend as well on the action of the same irritant which produced the fibrous changes in the liver as on the passive congestion resulting from them.

Chronic peritonitis, more or less general, in distinction from a few local adhesions, was found in 15[1] of these cases, in 3 of which it was associated with perihepatitis and perisplenitis, and in 1 with perihepatitis alone. Two others were complicated by perisplenitis and chronic pericarditis; 1 was complicated by pericarditis alone. In 13 ascites had been present during some period of their illness.

There were also 2 cases of acute peritonitis, both accompanied by ascites.

Local adhesions between the liver and neighboring organs were of frequent occurrence, and served in a number of instances as channels for the formation of a new vascular outlet, as was shown by the development in them of bloodvessels, at times of large size, but in a considerable proportion the veins described were so minute as to have been of little, if any, service, or else no mention of them is made.

A general perihepatitis, surrounding large portions, if not all, of the liver, and associated at times with a general thickening of its capsule, and in one instance leading to considerable hepatic deformity, was found in 13 cases.[2] They formed 25 per cent. of the cases in Class I., 31.2 per cent. of those in Class II., 8 per cent. of those in Class III., and 17.4 per cent. of those in Class IV. In 2 at least syphilis was a possible cause. Five were complicated by chronic nephritis, and one by adhesive pericarditis. Ascites was a feature

[1] Cheadle found 5 instances among 53 cases. (Loc. cit.)

[2] This is a decidedly smaller proportion than that given by Cheadle (15 out of 53), and probably depends on a question of definition of a general perihepatitis. (Loc. cit.)

in all but 1. In 2, however, it had not been present for six years, its disappearance dating in one from a single aspiration, in the other from an exploratory laparotomy.

Perisplenitis occurred 23 times; 4 times in connection with general perihepatitis. Seventeen of these cases were associated with ascites.

Dilatation of the veins having portal connections was noted but 29 times. A slight dilatation of the superficial veins might easily fail to be noted in the clinical examination, and a similar condition of the internal vessels, even when more marked might, from their collapse after death, escape detection, if it were not particularly looked for. This may account in part for the comparatively small proportion in which evidence of any attempt at the establishment of a collateral circulation was found. It was noted in almost exactly one-fourth of the cases in the first three classes (1/4, 4/16, 9/35 respectively), but in Class IV., where the obstruction was greatest, the proportion rose to nearly two-thirds (15/23). Although portal obstruction is unquestionably the important factor and the most obvious explanation of its development, it is difficult to account for its presence when the fibrotic process is slight unless some weakness in the walls of the vessels coexist. Such weakness is shown by the frequent occurrence of dilated cutaneous veins which have no connection with the portal system, and was demonstrated as well in the internal vessels of one of our cases, probably of syphilitic origin, in which, although the liver was but slightly affected (Class I.) and no other obstruction could be found, the azygos, postmediastinal, and esophageal veins were markedly dilated, and the patient died of hemorrhage.

Hawkins[1] says that as "dilated veins form a compensatory mechanism for the relief of the overcharged portal system, it may be surmised that when they are much developed and likely to give rise to severe hemorrhage there is not much tendency to ascites, and that clinical evidence agrees with this anticipation." This is not borne out by our figures, which indicate a very small value in such a mechanism, which either must have been originally inadequate or have become so later, since ascites and dilated veins with portal connections were associated in 22 of the 29 cases. The presence of enlarged vessels in the other 7 may have had some influence in pre-

[1] Allbutt's System, vol. iv. p. 179.

venting ascites, as all but 1 were found among the more advanced cases (Classes III. and IV.). Moreover, ascites and hemorrhage from the digestive tract were associated in 7 of the 9 cases in which dilatation of the collateral veins was described in the autopsy record as the source of the hemorrhage.

Ascites was present in 47 cases.[1] The direct effect of hepatic obstruction in its production is apparent, but unless other causes co-operate it is difficult to explain the almost constant proportion in which it appeared in the various classes, for it was found in 50 per cent. of the cases in Class I., in 62.5 per cent. of those in Class II., and 60 per cent. of those in both Classes III. and IV.

Weakness of the intra-abdominal vessels is probably an important factor in permitting the transudation of the blood serum. This may be due to the influence of the toxic agent of the disease as well as to the increased tension from portal obstruction. Hydremia is also not unlikely as an accessory factor, and while any one of these three causes alone may not be sufficient in the individual case, their combination, often in association with degenerative changes in other organs, may determine the presence of ascites and explain the absence of edema in regions where these different factors do not work in conjunction.

Chronic renal disease in the absence of general anasarca may be ruled out as a possible chief factor in producing ascites, though it may have acted as an accessory cause by producing hydremia. It occurred, however, in almost the same proportion among those with and without ascites, 28 and 29 per cent. respectively. The influence of cardiac disease was apparently quite marked, at least among the earlier cases, in some of which it was probably the chief cause, since it was present in 50 per cent. of those with that symptom in Classes I. and II., and less than 25 per cent. of those without. This ratio was not preserved in the later cases, the proportions in them being almost identical, 46 and 48 per cent. respectively.

The very large proportion of cases of peritonitis, perihepatitis, and perisplenitis, especially the two former, which presented ascites as a symptom, strongly suggest that they take an active part in its production,[2] but the evidence furnished by our cases as to the rôle played

[1] Dr. Price. Guy's Hospital Reports, 1883–84, Series 3, vol. xxvii. p. 295. Among 142 cases ascites occurred in 72 (50.7 per cent.).

[2] Compare W. Hale White. Guy's Hospital Reports, 1892, vol. xlix. p. 1.

by some form of chronic peritonitis is somewhat ambiguous, as the autopsy gave reason to believe that in a few it had been the most active factor in its disappearance. The recognition of the relative importance of the part in producing ascites which either of these two factors—hepatic cirrhosis or chronic peritonitis and perihepatitis—play may in a particular instance be difficult if not impossible. We may allude, however, to the poor nutrition which should accompany the pure hepatic cases and to the fact that fever was practically absent in them unless due to some complication. A history of febrile attacks and pain might, therefore, have considerable weight in suggesting the occurrence of previous attacks of peritoneal inflammation, while the nearer the aspirated fluid approaches the character of a typical exudate with its high specific gravity and large amount of albumin the greater is the likelihood of its presence. Hale White's observation that where ascites is due to cirrhosis alone the patients rarely live long, and seldom require more than one or two tappings at most, has a decided practical value in diagnosis if supported by sufficient evidence. It is corroborated in the main by our cases, but exceptions must be noted.

The length of life after the onset of ascites could be determined in only 25 cases. Fourteen lived less than six months, only 2 of which showed sufficient peritonitis or perihepatitis to be a factor in its production. Eight lived two months or less, in 1 of which there was general peritonitis and perihepatitis. Nine lived between six months and two years, in all but 3 of which one or both of these processes was well marked. The 3 exceptional cases survived, seven, twelve, and thirteen months respectively. One patient lived six years, and proved to have a general peritonitis at autopsy. The ascites had been cured by one aspiration. Another who lived the same length of time is later recorded as a successful case of laparotomy. General peritonitis and perihepatitis were found at autopsy, but were not mentioned in the account of the operation. It seems possible, in view of the exceptional nature of the case, that the surgeon's investigations stopped short of the liver, or that a peritonitis was not noted, owing to a lapse in the records.

Omitting from consideration the last 2 cases, from the difficulty of classifying them, a history of aspiration was obtained in 15 cases. Only 4 of the 10 in which it was done but once had either peritonitis or

perihepatitis, while 4 of the 5 cases where it was required more frequently showed one or both of these conditions.

Extravasation of blood into or from various organs either as a clinical manifestation or as an autopsy finding was a fairly common event during the last stages of the disease, and occurred as a result of a terminal infection or toxemia. Hemorrhage from the gastrointestinal tract sufficient to be clinically apparent was recorded but 15 times—12 from the mouth, with or without melena, and 3 from the anus alone. This may understate the true proportion in which this symptom occurred, as a number of histories were incomplete either as a result of the notorious reticence of hospital records on important subjects or because the patients entered too ill to give any account of themselves. The close relationship between the occurrence of hemorrhage and the stage of development of the cirrhotic process seems clear, as in every case but 2 the formation of connective tissue was well advanced (Classes III. and IV.). It is a noteworthy fact that some gross lesion to which hemorrhage could be attributed was present in all but 4 cases. In 3 of the latter its occurrence was entirely a matter of history, dating back six years in one instance, and no mention was made of the condition of the veins. In the fourth it was impossible to be sure from the patient's description that it came from the stomach. The source of the blood in the remaining 8 cases with hematemesis was from dilated veins near the lower end of the esophagus in 7, in 5 of which it was the immediate cause of death.[1] A gastric ulcer was present in the other. An esophageal varix was found in 1 of the 3 cases of simple melena, and in a second this was combined with another less extensive varix near the pyloric end of the stomach. Hemorrhoids were noted in the other case.

Jaundice occurred in 31 cases,[2] in 3 of which the presence of a stone in the common duct was a sufficient cause, while duodenitis, with plugging of the common duct, was found in a fourth. In the remaining 27 it was closely associated with the amount of connective-tissue increase in the liver, as only 1 (5 per cent.) of the 20 cases in Classes I. and II. presented this symptom, while it was found in 37

[1] R. B. Preble (American Journal of the Medical Sciences, Philadelphia, 1900, cxix. 263–280), in an analysis of 60 cases of fatal gastrointestinal hemorrhage due to cirrhosis, says that varices were present in 35 of 42 cases in which the esophagus was mentioned.

[2] The combined statistics of Price (loc. cit.) and Fagge (Guy's Hospital Reports, 1875, Series 3, p. 155) shows that of 202 cases jaundice was present in 64.

per cent. of those in Class III., and 56 per cent. of those in Class IV. It was usually a late and grave symptom, for while transient attacks extending over several years was mentioned in the history of a few patients, it became permanent in only 1 as early as one year before death. In 14 others in whom it was possible to approximate its onset it preceded death between four and eight months in 4. In the remaining 10 it had existed 2 months or less.

Carrington's[1] statement that fever not infrequently occurs as a result of hepatic cirrhosis finds little support in our cases, for a continuous elevation of temperature was never observed unless some acute process was present; but a sudden rise, lasting for a few hours, was occasionally recorded on the charts of patients who were under observation for a number of weeks. It rarely exceeded 100°, yet in one instance it touched 103.4°. It occasionally happened that the temperature remained normal or subnormal up to the day of death, in spite of some acute complication like pneumonia or acute endocarditis, yet a high temperature during the last few days of life was not uncommon as the result of a terminal infection.

The determination of the cause of death was beset with many difficulties, owing to the large number of pathologic conditions, both chronic and acute, which were found at the autopsy. Even with the assistance of the histories it was often impossible to tell whether the chronic complications had not so far outstripped the so-called primary disease as to have been the chief lethal factor, while in others death seemed rather attributable to a general degeneration than to a single cause. It was equally difficult to fix the relative importance of the acute complications, for while some undoubtedly were the direct cause of death, and some were with equal certainty only a mode of dying, others remained whose influence in terminating life could not be estimated. Nor could assistance always be obtained either from the size or microscopic appearance of the liver. Cases were found, as has already been mentioned, which showed a high degree of fibrosis, and yet had apparently suffered no discomfort from it, and extreme changes in weight occurred in both directions without producing symptoms of which the patient had complained. In one such case it weighed over 3000 grams, and in another, a man of forty-one years, only 980 grams. On a most liberal construction death occurred in

[1] Guy's Hospital Reports, 1883–84, vol. xxvii. p. 337.

41 as a direct result of the progress of the disease, including 5 due to esophageal hemorrhage. Seven died from what may be called the general effect of the toxic agent, as shown by degenerative changes in a number of organs, while 30 deaths were caused by incidental causes, 4 following operation for the relief of conditions not induced by cirrhosis. Eleven of the remaining 26 were due to other chronic diseases, and 15 to acute. Among the former tuberculosis was found 3 times, while among the latter acute endocarditis, which occurred 4 times, and pneumonia, which occurred twice, were conspicuous. Erysipelas, to which cirrhotic patients have been said to be particularly liable, occurred twice as the direct cause of death and once as an accessory, besides appearing in the previous histories of 3 other patients.

Fagge,[1] in a series of 130 cases, found that the average age of persons in whose bodies cirrhosis of the liver was discovered without the presence of marked symptoms during life was higher by about five years than that of persons who actually died of the disease, and argues that if this should be confirmed by a wider experience it would prove that cirrhosis is not always a progressive disease, but may remain stationary after reaching a certain degree of development. Rolleston and Fenton's statistics,[2] however, make the ages of patients dying with latent cirrhosis slightly younger than those who die of the disease. Our figures give the latent cases about two years more of life (47.5 to 45.7 per cent.), but this difference is too slight to be convincing.

The only important point in treatment on which a study of these cases can throw any light concerns the best method of relieving the ascites. In the enthusiasm which has followed the occasional success of a laparotomy the good results which have at times followed paracentesis, which was advocated forty years ago by Austin Flint,[3] seem to have been overlooked, yet a very considerable number is scattered through the literature in which relief of symptoms has been obtained for many years by simple aspiration. It is so frequently done solely as a measure of relief, without thought of effecting a cure, that a comparison of statistics of the two methods is impossible. The latest figures giving the results of surgical treatment with which we are

[1] Loc. cit.
[2] Birmingham Medical Review, 1896, vol. l. p. 193.
[3] British Medical Journal, 1883, vol. ii. p. 565. Flint confirms a statement made in 1863.

familiar are those of Brewer,[1] and are based on 60 cases, 2 of which are included in our series. We are able to add 3 others to this list, in 2 of which only an exploratory laparotomy was done. One died as the direct result of the operation, while a second died three weeks later from the progress of the disease. The third entered six years before her death and was tapped six times. She returned four years later, and the abdomen was opened, but as no abnormality was seen the wound was closed after the exploration. The ascites disappeared. Twelve were cured — that is, they lived from three months to about two years. One other required five tappings subsequent to operation before the ascites disappeared. Seven others were "improved," which, in the cases where this term is explained, meant less frequent tappings. Thirty-three died. Brewer admits that the operation is still in its experimental stage, and regrets the high mortality, which he attributes to the unwillingness of the majority of physicians to advise this method of treatment until it remains as the only hope of cure. A consideration of our cases, which tally well in their proportion of complications with similar series already published, may explain this unwillingness, for they show, as has already been brought out, that cirrhosis of the liver in a majority of cases is only one expression of the effects of some toxic substance on the general economy, and at the time when pronounced symptoms have appeared other important organs are usually already affected, often to such a degree that the cause of death is difficult to determine, or, in their rare absence, the glandular structure of the liver has been so far destroyed as to cut off all expectation of recovery. Furthermore, ascites, which has been the determining factor for operation in almost every case, is, with rare exceptions, when due to the liver alone, a late symptom.

The conclusion seems reasonable that operative measures are never justified in the presence of jaundice, and rarely with a history of hemorrhage from the digestive tract, since the fibrotic changes in the liver are probably so far advanced as to cut off expectation of greatly prolonging life; but where, with practically a sound heart and kidneys, the general nutrition is so well maintained as to show that sufficient glandular structure still remains in the liver to maintain its

[1] Medical News, February 8, 1902.

functions, and where competent medical treatment has failed operation may be considered. Yet the proportion of favorable cases must be very small, and nature's failure to secure results save in exceptional instances by methods which the surgeon imitates does not diminish the difficulty of proving that the operation is a justifiable one. The cases in which surgical treatment has been effectual are, with few exceptions, so incompletely reported as to leave great doubt as to the importance of the part played by the liver in the production of ascites. The most that can be said is that certain cases of ascites are cured by the surgeon either by a simple laparotomy or by a more complicated operation, and that in some of them hepatic cirrhosis existed.

Although dangerous symptoms have followed paracentesis none were recorded among our cases; but we would refer to an experience of one of the writers, which is interesting from the enormous amount of fluid which was obtained. The patient's condition was hopeless, and at his earnest solicitation the abdomen was emptied on each occasion. During the last two months of his life between 60 and 72 quarts were three times withdrawn. Death took place from cerebral anemia three days after the last tapping.

The more important conclusions drawn from the analysis of these cases may be summarized as follows:

Hepatic cirrhosis is, in a majority of instances, but one expression of the effect of a systemic poisoning. The degenerative changes in other organs are to be regarded as part of this general process rather than as complications.

The splenic tumor and dilated veins are due in part to portal obstruction, but also seem dependent on the underlying toxic cause, since they are occasionally associated with slight hepatic changes.

Dilatation of the vessels may have some effect as a compensatory mechanism, but is rarely adequate to prevent ascites.

Persistent jaundice and hemorrhage from the digestive tract seldom occur until the connective-tissue formation is well advanced.

Hemorrhage was found to be almost invariably due, when a full pathologic description was given, to some gross lesion, which in most cases was an esophageal varix.

Ascites occurred in practically the same proportion of cases in all four classes, and was a late symptom. Its early appearance was, with

rare exceptions, associated with some form of peritoneal inflammation.

Continuous fever was never found except in the presence of complications. A brief elevation of temperature occasionally occurred for which no cause could be discovered.

No evidence was found to show that the course of the disease was not always progressive, but a high grade of cirrhosis was sometimes reached without incapacitating the patients.

Surgical treatment may be indicated in a very small proportion of cases, but conclusive evidence is still lacking to show that the ascites in the cases successfully operated upon was due to hepatic cirrhosis, and not to coincident conditions.

CLINICAL MANIFESTATIONS OF THE EARLY STAGES OF CIRRHOSIS OF THE LIVER.

By FRANK BILLINGS, M.D.,
OF CHICAGO.

In my ambulatory practice, especially in the office, I have been surprised to find a relatively large number of patients who have applied for relief of various symptoms in whom a palpable, usually tender and enlarged liver could be demonstrated. The symptoms in the main were in many patients those of neurasthenia; in others myalgia or a mononeuritis, or, most frequently, some gastrointestinal disturbance. In a few cases arthritis was complained of, and the affected joints showed evidence of that trouble.

The following is a case in point:

Case I.—B. M. F., aged fifty-four years, male, lumber dealer; residence, Chicago. His father died of tuberculosis. No other history of inherited disease in the family. Has used alcohol to a very moderate and irregular degree. Smokes moderately.

The patient had typhoid when fifteen years of age, from which he made a good recovery and enjoyed perfect health until about twenty years ago. Since that time he has had more or less rheumatism, as he terms it, affecting the muscles, especially of the back, and fifteen years ago he had pain in the left shoulder, and the arm was almost helpless. During the last year he has had pain in the right knee, which was at first swollen and painful, and later painful when walking or when the leg was extended and flexed upon the thigh. He has been upon a diet almost free from meats for the last eight months, and the knee has improved somewhat under the regimen used. He spent a considerable time at Hot Springs, Ark., last spring without relief.

Examination showed a well-preserved man. The chest was negative. The liver dulness extended from the sixth rib in the mammary line to below the costal arch, and its lower border was palpable, its edge sharp, the consistency increased, and tenderness was marked upon firm pressure. The tenderness was felt not only at the point of pressure in the mammary line, but caused also a sharp pain in the epigastrium.

This reflexion of the pain of a tender liver to the epigastrium when the right lobe was pressed upon below the costal arch was noted in several other cases.

The spleen was not palpable; knee jerks present. There was distinct crepitus in both knees upon passive flexion, and extension was more marked in the right knee than the left. The right knee was slightly larger than the left, and there was slight tenderness over the joint when firm pressure was made, with flexion and extension of the leg.

The urine (specimen): Specific gravity, 1022; acid reaction; no albumin, no sugar, no casts; urea, 2 per cent.

The diagnosis of chronic interstitial hepatitis with autointoxication and resulting arthritis was made.

The patient was placed upon a diet free from the red meats, and allowed no sweets. A flannel bandage was ordered for each knee, and he was told to exercise daily by walking and to also forcibly extend and flex the knees morning and evening while lying on his back.

The medication ordered was ten-grain doses of ammonium muriate after meals, with a sufficient amount of sodium phosphate in hot water on rising, to move the bowels daily.

On January 30, 1901, the patient was re-examined and found much improved. The liver was still palpable, but less tender and apparently less indurated. There was much less crepitation in the knees. The general management and the medication were continued. On May 11th the patient was again examined, when he complained of some dragging, aching pain in the right hypochondrium, with considerable gaseous eructation and epigastric weight after eating. The physical findings were about the same as upon the last examination.

On July 11th the patient complained only of itching of the skin, which was associated with severe sweating incident to the hot weather. The liver was less large, less tender, and less indurated. He was given twenty-grain doses of sodium bicarbonate after meals.

On October 11th the patient expressed himself as feeling perfectly well. The liver could be felt as a mass descending with inspiration, but its edge could not be felt, and it seemed normal in consistency and was not tender. There was no crepitation in the knees and no lameness.

On December 3d the patient was seen for the last time. The physical findings were negative, as at the time of the last examination. He complained of some fermentative dyspepsia, but otherwise was well. The urine at this time gave a specific gravity of 1022; acid reaction; no sugar, no albumin, no casts.

He was advised to continue the diet ordered when first seen, to take a good deal of out-door exercise, and to drink water freely as a diluent on rising and three or four hours after each meal.

The case is quoted in full as a not unusual one of a group I shall report—in the history he presented, in the physical findings, and in the very favorable results noted.

I wish to say at this point that I do not quote this case as one

showing a beginning chronic interstitial hepatitis which was cured by the management noted. It would be very intemperate to say that this case and the others which I shall report were all cases of hepatitis, and that in this and in some others a cure occurred. It is reasonable to suppose that the proliferation of connective tissue which occurs in hepatitis does not resolve. It is probable that the improvement in the physical condition of the organ noted was not due to the removal of the inflammatory products, but the relief only of the hyperemia incident to the condition.

It may be well to note at this point that in health it is difficult to palpate the liver. A liver of normal consistency and size, with not abnormally thick abdominal walls, may be felt as a mass descending against the palpating hand below the costal arch in the anterior axillary line. One cannot feel its edge, and would not know by the feel that it was a liver without the knowledge that the liver usually occupies that situation. With an abnormally thick abdominal wall even this descending mass cannot be felt upon the deepest inspiration.

If one can make out the edge of the liver or can palpate the mass which can be recognized by its contour as the liver, it is not a normal one, but is increased in its density and is usually large, although it may be smaller than normal. A palpable liver edge can usually be recognized by the notch in the anterior border which marks the point of separation between the right and left lobes.

A symmetrically enlarged and sharp-edged palpable liver is not necessarily a cirrhotic one; that is due to an increase in the connective-tissue element.

Passive congestion from a weak right heart, bile stasis from obstruction of the common or hepatic ducts, fatty or amyloid infiltration may present the same contour and consistence of the liver.

The smoothness of the surface of the liver in the early stage of cirrhosis may also resemble the enlargement of the liver due to the conditions named.

Again, one cannot state that a cirrhotic liver is in the first stage because it is palpable, indurated, sharp-edged, and even tender, for we know that collateral circulation may occur in many of the cases of cirrhosis of the liver, and the venous obstruction and consequent abdominal dropsy, which are so characteristic of the late stage of the disease, may be postponed indefinitely or not appear at all.

Collateral circulation may occur through an enlargement of the deeper veins, too, without an enlargement of the branches of the epigastric and of the internal mammary veins, which are so often noted enlarged in cirrhosis of the liver with dropsy. The deeper veins which take part in the establishment of collateral circulation are the veins of the suspensory ligament, the diaphragm, the azygos, the esophageal, and the gastroepiploic. If the collateral circulation so established is sufficient, dropsy will not occur, and even the superficial veins of the abdomen may remain slightly if at all enlarged. In these cases, therefore, the symptoms will be chiefly due to the intoxication incident to the cirrhosis of the liver; while the venous obstruction, which usually gives rise to dropsy of the peritoneum and to enlargement of the superficial abdominal veins, will remain absent. It is true that hemorrhage from the stomach due to a rupture of the enlarged veins of the stomach wall or of the esophagus may occur as a symptom of the venous obstruction, and this, too, in a relatively early period of the disease.

In presenting these cases I have excluded all cases of palpable liver associated with diabetes mellitus, of heart incompetency with chronic venous stasis, of Bright's disease with associated cardiac weakness and venous stasis, of gallstones or other disease obstructing the bile ducts, with consequent bile stasis, and of all cases of cirrhosis with evidences of portal vein obstruction.

The cases were, therefore, selected as probable ones of the primary stage of cirrhosis, because: 1. The liver was palpable, enlarged, usually tender to the touch, and had a sharp, indurated edge. 2. Because of the absence of evidence of other causes of enlargement and induration of the liver. 3. Because of the absence of evidences of portal obstruction.

Two cases while under observation developed ascites, and were, therefore, recognized in the early stage.

During the last three years fifty-four patients have presented themselves with the conditions of liver named above. Of this group all were males. The ages ranged from thirty to sixty years. Eleven were from thirty to forty years; twenty-five were from forty to fifty years; eighteen were from fifty to sixty years.

The ages of the groups correspond to the ages in which atrophic cirrhosis usually occurs. Three were saloon-keepers and one a brewery

agent. The remainder had varied occupations which could have no relation to the disease. One only confessed that he had suffered from syphilis, and in none was evidence of syphilis found. Three had suffered from gonorrhea. Twenty-five, or almost one-half the number, confessed to the use of alcoholic beverages, usually whiskey in excessive amount—that is, from six to twenty drinks a day. Eighteen, or 33 per cent., admitted using alcoholic beverages in small amounts—that is, from one to three drinks daily—or of taking it at irregular intervals in small amounts. Eleven, or about 20 per cent., denied the use of alcohol at all, and in the case of some of them I know the statement to be true. Twenty per cent. is a large number to suffer from atrophic cirrhosis not due to alcohol.

In the non-alcoholic group of eleven cases I was unable to trace any other cause for the cirrhosis, as, for example, lead poisoning, malaria, previous acute infectious disease, etc. The majority of the cases sought consultation for some form of disturbance of the digestive tract. Fifteen had morning nausea and vomiting. This is a form of disturbance common to cirrhosis in all cases, and is doubtless due to catarrhal gastritis. The following case illustrates this condition:

CASE II.—J. M., aged thirty-two years, single, no occupation, presented himself November 20, 1900. Family history good. He had had the acute diseases of childhood, but had always been strong and healthy and recovered quickly from simple acute infections. Had taken exercise.

Several years ago he was a hard drinker, using from three to fifty drinks a day. He smoked moderately. He had suffered from gonorrhea, but never had syphilis. He had acute articular rheumatism in 1896.

He sought the consultation for stomach trouble. This began while he was drinking, and manifested itself by pain and a sense of heaviness and fulness in the epigastrium after meals. Occasionally there was morning nausea, with gagging and coughing up of slimy mucus. There was much flatulence, and the bowels were inclined to be loose. The appetite was usually good. He had less strength, endurance, and energy than formerly. He complained of pain in the back, aggravated by stooping, and also a sense of heaviness in the region of the liver. His weight was ten pounds less than two years before.

Examination showed some tenderness in the epigastrium; the edge of the liver palpable below the costal arch, moderately hard and tender. The upper line of dulness began at the sixth rib, in the mammary line. The heart and lungs were negative. The spleen was not palpable. The urine: specific gravity 1009, pale straw color, acid reaction; no albumin, no sugar, no casts.

He was placed upon a diet free from sweets, greases, and rich mixtures,

and was given hot water a half-hour before each meal. Ammonium muriate in ten-grain doses was used after meals, and sodium phosphate in hot water when necessary as a laxative in the morning.

The patient returned on January 14, 1901, and said that he was very much improved under the management advised, and remained so until recently, when he again drank alcohol to excess. Since that time he has had a return of the old symptoms. The physical condition was practically as upon the first examination, although the liver was somewhat more tender.

The same treatment was continued. On May 24, 1901, the patient reappeared and stated that he was in perfect health. The liver edge was still palpable, but not tender, but could only be felt at the end of a deep inspiration.

This case was an undoubted one of alcoholic cirrhosis in the early stage, and there can be no question that many of the symptoms of which he complained were toxic in character. The relief was doubtless due to better hygiene and also to the more temperate use of alcoholic beverages.

Gastritis is commonly found also in alcoholic abuse, with or without evident cirrhosis of the liver. Congestion of the bloodvessels of the stomach from portal stasis from any cause may also produce morning nausea and vomiting. Twenty-three others of the group suffered from fermentative dyspepsia, manifested by epigastric weight, pain, and tenderness, with eructation of gas, flatulence, etc. The following is a case in point:

Case III.—A. T., aged thirty-two years, married, sewer contractor, presented himself November 28, 1901. His family history was negative. His health had always been good until the present illness. He had not used tobacco or alcohol. Denied venereal disease.

He complained of fulness and weight, with belching of gas one to one and a half hours after meals. With this was a sense of weakness and some pain in the epigastrium; occasional lumbar muscular soreness and headache, which lasted for several days at a time. Appetite was poor and the bowels constipated. Had lost ten pounds in weight during the past year.

Examination showed a fairly well-nourished man. Negative findings in the head and neck. Lungs negative.

The heart dulness extended from 1½ cm. to the right of the sternum to 2½ cm. to the left of the left nipple; the upper border to the third rib. The apex-beat in the fifth interspace 2 cm. outside of the left nipple. The pulmonic second sound accentuated. The liver extended from the sixth interspace in the mammary line to one finger's breadth below the costal arch; its edge was easily palpable and tender, and the consistency of the liver was increased. The spleen was not palpable. A single specimen of urine

was amber colored, acid reaction; specific gravity, 1025; no albumin, no sugar, no casts.

A diagnosis of hepatitis with resulting toxemia was made and patient was placed upon a simple diet, without sweets or greases, and with plenty of hot water between the meals. He was given dram doses of sodium phosphate in hot water on rising in the morning, with the misturæ rhei et sodæ, 2 drams after meals.

On December 19, 1901, the patient again presented himself and expressed a sense of much improvement in health. The digestive disturbance was practically gone; the bowels were still constipated, but moved with the sodium phosphate. The liver was found still somewhat enlarged, its edge sharp and tender. The patient has not been seen since that time.

As this patient had a mitral insufficiency, the question would naturally arise, Was the liver condition due to passive venous stasis? This was probably not true, because there was no sign of broken compensation. The lungs were clear, the spleen was not palpable, and the urine was normal.

Thus thirty-eight, or about 65 per cent., suffered from disturbance of the digestive tract, chiefly of the stomach. Twenty-six were constipated, requiring the use of medicine to move the bowels. Four suffered from diarrhea. Three had alternation diarrhea and constipation. Twenty-one had regular daily bowel movements. Three only of the group suffered from hemorrhoids.

Hemorrhoids in cirrhosis of the liver is not an uncommon result of obstruction of the portal circulation. It is also claimed by some writers that an associated rectal tenesmus is a not uncommon symptom of the beginning of obstruction of the portal circulation. I was surprised to find that so few of this group suffered from an enlargement of the hemorrhoidal veins.

Next to the disturbance of the digestive tract the most common complaint was of muscular rheumatism, so called. Twelve suffered from lumbago, for which they sought the consultation. Nineteen suffered from muscular soreness elsewhere in the body, usually, however, combined with lumbago. Two suffered from sciatica and two from musculospiral neuritis. Five suffered from severe headache, usually associated with symptoms of stomach disturbance. Two suffered from arthritis of both knees, which had been diagnosed and treated as rheumatism. Eight presented classic symptoms of neurasthenia—that is, lethargy, lessened strength and endurance, nervousness, sleepiness during the day, and insomnia at night.

The following case illustrates the neurasthenic element:

CASE IV.—B. C., aged forty-five years, single, lumber dealer, residence in State of Mississippi, appeared on January 16, 1901. Mother died of cancer of the breast and the father of pernicious anemia at sixty-eight years. The patient smoked to excess both cigars and pipe. He had used from one to six drinks of whiskey a day for several years. Denied venereal disease. Recalled no acute disease during his life. For six years had been working thirteen to fourteen hours a day and taking practically no vacation and no recreation.

About one and a half years ago he began to be irritable and nervous, and these symptoms became worse with time. For six months had pressure at the base of the brain, with a sense of heat, numbness, and tingling of the skin in places. He had less strength and endurance than formerly, and suffered from shortness of breath and palpitation of the heart upon exertion. He was much annoyed by a sense of pressure over the sternum, often sleepy during the day, and suffered from insomnia at night. Was more emotional than formerly. Had a good appetite usually, but suffered from morning nausea and regurgitation of fluids and gas, especially after eating. Bowels were sluggish. Had paid no attention to the selection of foods in his diet, and had eaten all sorts of greases and indigestible food. His weight was 136 pounds, average being 155.

Examination. Poorly developed, thin of flesh. Pupils reacted slowly to light and accommodation. Chest negative. The liver edge extended from the sixth rib in the mammary line to one inch below costal arch, where it was easily palpable. The edge sharp and tender, and liver density much increased.

The blood showed no plasmodia of malaria; the spleen not palpable.

The Urine. Specific gravity 1013, pale, alkaline; no albumin, no sugar. Earthy phosphates were deposited.

He was advised to remain North and rest from his business, to take a simple diet, with cold baths in the morning; to stop entirely the use of alcoholic beverages and to diminish the amount of tobacco. A saline was given in hot water on rising in the morning, and he was given the misturæ rhei et sodæ 2 drams before meals.

On January 31st the patient stated he had had two chills in one afternoon since his last visit, but that he had been very nervous at the time, and the chill was not followed by any perceptible increase in temperature and no sweat. He slept better, the appetite was improved, and the weight increased two and a half pounds. The physical examination presented the same conditions as upon the first examination.

On February 14th the patient was still more improved; there was no nausea, and the digestion was practically normal. The bowels were still sluggish and the stools not formed.

On March 4th the patient presented himself for an acute coryza, but stated that his general condition was very much improved as compared with his condition when he first began treatment. His weight had increased

five pounds. The liver was still palpable, but much less tender. Treatment was continued.

This patient's condition was no doubt due to his overwork and especially to his habits of life and the alcoholic misuse. There was doubtless an alcoholic gastritis and there was certainly a hepatitis. The improvement was very marked and steady from the beginning of the improved hygiene. The symptoms were doubtless due to the toxemia incident to the liver and stomach condition, but probably more to the defective liver than to any other cause.

Five suffered from chronic pharyngitis, which is not uncommon in alcoholism, and three had chronic bronchitis. Thirteen complained of dragging sensations and soreness in the right hypochondrium, which was aggravated by long standing and increased by palpation of the liver, and was usually relieved by lying down. Tenderness of the liver was found on palpation in the thirteen named above and also in some of the remaining group who did not suffer from the dragging sensation and tenderness in the right hypochondrium.

The urine was normal in forty-two cases—that is, it contained no abnormal elements. The specific gravity was not high, as a rule, contrary to the condition usually found when the portal circulation is obstructed. The highest specific gravity was 1027. In only two cases was the specific gravity below 1010. In all the cases examined the total solids and total urea excreted were within normal limit. A trace only of albumin was found in twelve cases, and this was usually associated with the presence of hyalin, and, in three cases, of granular casts.

Chronic interstitial nephritis is not an uncommon association with cirrhosis of the liver of alcoholic origin, and evidences of a mild degree of nephritis in twelve of the cases is therefore not surprising.

Glycosuria ranging from a trace to 0.8 per cent. was found in four cases, but there was no polyuria, no hunger or thirst, and no wasting. The following is one of the four cases:

CASE V.—J. J. E., aged fifty-eight years, married, railroad master mechanic. Was first seen on November 17, 1900. A brother died at forty-eight years, of diabetes. Family history otherwise negative. He had used tobacco very moderately, but none for several years. Had used a little alcohol in the form of beer and wine. Denies venereal disease. Had typhoid fever at

twenty-two years and pneumonia at fifty-three. Has always worked hard, and has usually been in good health. Eighteen months ago he noticed that he became more easily tired than usual and had gaseous fermentation, with slight constipation. He voided the urine naturally and in not increased amount. His physician found sugar in the urine, but did not state the percentage of sugar present. He spent the summer of 1899 at Carlsbad and returned very much improved in general health.

He now complains of lessened endurance and fatigue which comes with but little physical exertion, and his work makes him nervous and fretful. He has a moderate appetite, with some gaseous indigestion and no special thirst. He uses a mixed diet, with less starch than he used before the discovery of sugar in the urine, and uses claret or beer once a day with his meals. He uses both tea and coffee. His work requires him to be much out-of-doors, and he is filling his position as a master mechanic for a railroad, but says that he is not as able to grasp the details of his work as formerly. His present weight is 174 pounds, while eighteen months ago it was 190, his usual weight.

Examination shows a well-built, fairly nourished man. Tongue furred and slightly brownish in color. Pulse 70, regular, tension somewhat increased. Slight sclerosis of the palpable arteries. The heart dulness is one-half inch within the nipple line at the left, the base at the third rib, and the right border at the right sternal edge. There is a faint apex systolic murmur, made more manifest by a little exercise, which is not transmitted into the axilla. The aortic second sound is somewhat accentuated. The lungs are negative. The liver dulness begins at the sixth rib, in the mammary line; the edge is palpable, sharp, firm, and tender two inches below the costal margin; the spleen not palpable. The abdomen is otherwise negative. The urine: 1000 c.c. in sixteen hours, yellowish color, reaction acid; specific gravity 1027; a trace of albumin and 0.8 of 1 per cent. of sugar, 2.4 per cent. of urea, or 24 grams in sixteen hours. Solids for sixteen hours, 63 grams, of which 8 grams are sugar.

Patient was placed upon a better hygiene in reference to food, the starches and dark meats diminished, and the alcoholic beverages taken away, and he was given strychnin 1/50 grain before meals, with ten drops of a 1 per cent. solution of arsenic bromid after meals.

On December 28, 1900, the patient presented himself much improved. The amount of urine in twenty-four hours was 1800 c.c., reaction acid, specific gravity 1022, very slight trace of albumin, 0.8 per cent. of sugar, 1 per cent. of urea, no casts. His weight at this time was 173 pounds, his appetite good, his bowels regular, and he made less complaint of neurasthenic symptoms. The liver edge could still be distinctly felt, but was not as tender as when first examined.

On May 4, 1901, there was 1200 c.c. of urine, specific gravity 1027, slight trace of albumin, 0.2 of 1 per cent. of sugar, 2 per cent. of urea, no casts. He had lost four pounds in weight; otherwise there was nothing new. Treatment, both hygienic and medicinal, continued.

On July 12, 1901, the amount of urine was 1500 c.c., normal color, reaction acid, specific gravity 1023, a very slight trace of albumin, a trace only of sugar, urea 2.4 per cent., and the sediment contained a few uric-acid crystals, but no casts. His weight at this time was 170 pounds, with a general improved subjective condition. There was a complaint, however, of pain and tenderness in the region of the right musculospiral nerve and slight lumbago. The liver edge could still be felt, and there was slight tenderness remaining. He was given ten-grain doses of ammonium muriate with the strychnin, as before, while the arsenic was discontinued.

On September 14, 1901, the amount of urine was 1400 c.c., reaction acid, specific gravity 1021, no albumin, sugar very faint trace, urea 1.6 per cent., a few hyaline casts, and a few uric-acid crystals. The liver area was still slightly increased, and the induration and very slight tenderness still remained. The musculospiral neuritis was practically well. He complained only of slight gaseous fermentation in the stomach.

On October 19, 1901, the urine was 1700 c.c., acid, specific gravity 1024, slight trace of albumin, 0.6 of 1 per cent. sugar, urea 1.6 per cent., a few granular casts, a few crystals of calcium oxalate, and a few sugar spores. The patient felt well, appetite and digestion good, bowels regular, and he presented himself at this time because he desired to have a re-examination. The liver area was still increased in size, with some induration, but no tenderness. He had not been quite so careful with his diet, and hence the slight increase in the amount of sugar in the urine. He was again placed upon the arsenic bromid solution, ten-drop doses after meals, while the general management was continued.

This patient would possibly be called a chronic diabetic, but at no time in his history had he a polyuria, and the condition of the liver was such that the anatomic diagnosis of cirrhosis was justifiable. Furthermore, he suffered from toxemia, due, doubtless, to the liver condition. This toxemia manifested itself in a neurasthenic state, in myalgia, and in a neuritis. I also believe that the glycosuria was due to the liver condition.

It is a well-known fact that sugar may appear in the urine in cirrhosis of the liver, and cirrhosis is one of the causes given of diabetes. It is also true that an induration of the liver with proliferation of connective tissue and degeneration of its cells occur in diabetes.

Bile, a trace only, was found in three cases, and was not constant in the three, as it was not found after the first examination.

Microscopic blood was found in two cases, and in one of these pus was present. The symptoms in both of these patients pointed to urinary calculus.

The spleen was palpably enlarged in four cases. It is known that the spleen is usually palpable in cirrhosis of the liver, and is due frequently to the venous stasis. It is also true that the spleen may be enlarged from the toxemia, due to the cirrhosis or from the infection to which the cirrhosis is due.

Myocarditis occurred in four associated with arteriosclerosis of the palpable arteries. There was a mitral systolic murmur in three, and aortic systolic murmur in two, and a systolic murmur in the pulmonary area in two. Inguinal hernia occurred in three, and there was a palpable right kidney in four of the patients.

The existence of arteriosclerosis and cardiac disease in a few of the group had no causative relation to the liver condition, I think, because the heart was competent in all of the patients examined.

The presence of calculi in the urinary tract was probably accidental, although it would be consistent to believe that the liver cirrhosis would result in malassimilation, possibly leukocytosis, with an increase of uric acid, and consequently a deposition in the previously bacteriologically infected kidney.

Cirrhosis of the liver gives rise to symptoms which depend upon two conditions: first, those due to portal obstruction; and, second, those due to intoxication in consequence, apparently, of the failure of the diseased liver to modify the products of digestion and the other material absorbed from the digestive tract.

The toxemia is further intensified, doubtless, by the passage of the toxic material from the digestive tract directly to the blood through the collateral circulation.

Symptoms of cirrhosis of the liver are therefore usually referred to as obstructive and toxic. It has appeared to me that the symptoms in the cases presented could be rationally interpreted as due to a toxemia in consequence of the changed anatomy of the liver.

It may be maintained by some that the symptoms noted in these cases occur in patients who have no recognizable change in the liver. Many attribute similar and like symptoms to toxemia from gastrointestinal disorders, with faulty liver action, without recognized anatomic defect, or to uric acid in excess from faults of the table, or to defective excretion of waste material through the bowels, skin, and kidneys. I shall not attempt to oppose these propositions.

As stated above, the cases are presented with a statement of the

positive, anatomic, clinical findings, and with the subjective symptoms for which the patients sought the consultation. It may be true that the symptoms were not due to the changed anatomy of the liver, although, as stated above, the coincident improvement in the liver condition with the disappearance of subjective and objective phenomena was striking in some cases.

It is also true that the improvement occurred most markedly in those patients who followed the general management advised, in the way of abstinence from alcoholic drink, in a regulation of the diet to a very simple one, in the adoption of physical exercises or other recreation, and in the use of water as a diluent drink; that the improvement was also coincident with and in direct ratio usually to the improvement in the elimination of waste through the bowels, skin, and kidneys.

Admitting this, it does not alter the proposition that the symptoms were due to or at least aggravated by changed liver structure. The admitted autointoxication associatied with the indigestion of gastritis, or of neurosis of the stomach, or of the toxemia of constipation, etc., would rationally be intensified by a crippled liver.

The fact noted in several cases of improvement in the liver condition with the adopted better hygiene is important.

In these cases the commonly associated digestive disturbance was improved or disappeared. Would it be fair, therefore, to believe that the liver condition was due to the abnormal condition of the digestive tract? If so, was the improved liver condition due to the bettered state of the stomach and bowels? If this is granted, one would rationally believe that a beginning liver cirrhosis was checked.

Unfortunately, we do not know the nature of the toxin which occurs in cirrhosis of the liver; nor do we understand what the poison is which occurs in autointoxication from indigestion due to disease of the stomach and bowels, or to faulty diet, or to constipation, etc. Consequently our deductions, be they never so rational, are not truly scientific, and are consequently open to controversy and criticism.

The treatment followed in the cases reported was an attempt in each case to find the hygienic faults. The diet chosen was made free of heavy meats, of rich mixtures, of greases and sweets, and of much fluid with the meals. Alcoholic drink was prohibited. Water was advised as a diluent on rising and three or four hours after each

meal. Recreation, in the true sense of the word, was advised for each. This in the majority consisted of out-door work or play.

The medication followed was indifferent, but the principle followed was to keep the bowels free with the use of a saline in hot water one-half hour before breakfast; the misturæ rhei et sodæ (U. S. P.), with or without tincture of nux vomica, in doses of from two to four drams before or after meals.

Digestive ferments were not used. When deficient hydrochloric acid was found in the stomach contents it was given after meals.

Ammonium muriate in ten-grain doses was used in some cases, because, in the writer's experience, its use in cirrhosis of the liver has been coincident with improvement in the liver condition in many cases.

Kussmaul, many years ago, advised the use of ammonium chlorid in the early stage of cirrhosis, and I have used it much since that time.

However, in the light of a considerable experience it is my belief that an improved hygiene with the use of a saline purgative when it is necessary will give results quite as good without as with the use of drugs.

DISCUSSION.

DR. PACKARD: I suppose that all of us have at times written papers which we would like to recall in order to modify the statements made. I feel now that if I could do it I would like to change some of the statements made in a paper that I wrote with Dr. Le Conte on "The Surgical Treatment of Cirrhosis of the Liver." In this paper we recorded two cases, both of which ended fatally. I believe that in one of our cases before I turned the man over to the surgeon I should have studied more the functional capacity of his kidneys. Unfortunately, I was satisfied with the ordinary routine clinical examination. The patient died within forty-eight hours after operation from profound toxemia. While the examination of the urine showed no gross evidence of renal disease, I do not think that I sufficiently realized the greater call that was to be made upon them when the portal and the venous systems were united in the same way, but not to so great an extent as is the case when an Eck's fistula is formed for experimental purposes. Our patients with cirrhosis of the liver usually die not from ascites but from toxemia, and it seems to me that we must in some way try to formulate rules for our guidance in

determining in just what cases the artificial establishment of a collateral circulation is justifiable.

DR. DANFORTH: I wish to emphasize the suggestion of the last speaker in reference to the examination of the urine. I believe it is a rare case of cirrhosis of the liver in which the kidneys are not involved. I recall a case now where there was enlargement of the liver and commencing cirrhosis, with every evidence of cirrhosis of the kidneys also, and I think we should always take that into account. Moreover, there is always more or less indication for the use of diuretics to help in the elimination by way of the kidneys. Dr. Billings has alluded to his use of ammonium chlorid and its recommendation by Nothnagel as an efficient remedy in hepatic cirrhosis. I heard this salt lauded by Prof. Edward E. Phelps, of Dartmouth Medical College, for the same purpose more than forty years ago, and have employed it more or less ever since, although in most cases I think sodium iodid more efficient.

DR. SMITH: I want to relate a case seen fifteen years ago, in which the amount of ascitic fluid was greater than I have ever seen before or since. It pretty nearly filled an ordinary wash-tub. I found the patient in a condition of extreme distress from the immense accumulation and the proposed paracentesis, but he had been told by his physician that he must not submit to any operation. I communicated with his physician, but he replied by telegraph that he would not permit an operation. Finally, however, the condition became such that I assumed the responsibility of evacuating the fluid. For about a week the wound remained open, but then closed, and about a month later there was no tendency to reaccumulation. I then lost sight of the patient, and believing that he could not restrain his appetite for drink I supposed he would soon die. At the end of about four years I unexpectedly met him on Fifth Avenue, a slender, ruddy, healthy man, and on inquiry I found that he had succeeded in controlling his habits and had had no further trouble during that time. Three years later he came to my office with an accumulation again, but very moderate in amount. Under the use of potassium iodid it slowly disappeared, and though I have not seen him since I have not heard of his death, although I think I should had it occurred.

DR. HERTER: While I agree with Dr. Packard in his belief in the importance of toxic influences, I do not think that fact alone should discourage us in undertaking operative measures to improve the circulation of the liver, which may of itself tend to relieve the toxic condition. I want to call attention to the fact that even in the extreme degrees of cirrhosis the liver is still capable of carrying on considerable activity. Experiments have been made with ammonium carbonate on patients with advanced cirrhosis of the liver, the idea being that the organ was no longer able to synthesize in urea the carbon dioxid and the ammonia given off in the process of metabolism. Under such circumstances we would expect that the patient would have an

increase of ammonia in the urine, but these experiments showed that even up to the most advanced stage of the disease the liver could dispose of large quantities of ammonium carbonate, converting it into urea in the normal way.

DR. JACOBI: I would speak of what appears to me an important case, in which it was assumed that the establishment of a collateral circulation terminated in a temporary recovery. Nearly forty years ago I treated a grocer in Church Street, New York, a hard-working and hard-drinking man of forty years. His ascites required paracentesis every few weeks. Having seen many cases of hydrocele and occasionally large cysts getting well with iodin injections, I was naive enough to believe that this ascites might be treated in the same way. I builded better than I knew. My iodin injection into the free abdominal cavity resulted in a fearful and nearly fatal peritonitis. But he got well and went to work again, stopped his drinking, possibly from fear of me, and lived several years without a return of his ascites.

A PRIMARY CARCINOMATOID TUMOR (MESOTHELIOMA) OF THE ADRENALS, WITH SARCOMATOUS METASTASES.

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The following case, which presents such interesting features, was admitted to the Royal Victoria Hospital in the service of Dr. Stewart, on September 3, 1901. Dr. Stewart has kindly permitted me to report the case, and I wish to express my gratitude to him for this and numerous other courtesies.

The case was that of A. F. I., a machinist by trade, aged forty-two years. His family history was unimportant. He had led a fairly regular life, and was a strong, healthy man. He had no venereal history, but had had typhoid fever when he was twenty-seven years old.

In June, 1901, while at work, he had a peculiar "attack," in which he became unconscious, a state which lasted about twenty minutes, and during this he had some inspiratory distress. Following this attack he was weak and could do only light work. A month later he had another and similar one, which he could feel coming on for about two minutes previous to the seizure. He had had no other attacks. Two weeks before admission to the hospital he began to suffer from headache, which was confined principally to the left frontal region. This lasted until September 1st, and did not recur. On this and the following day he vomited after taking medicine, and about this time began to be conscious of some dimness of vision. Since August 30th he had been rather drowsy and stupid; no particular weakness had been noticed, and no muscular twitchings. At the time of admission to the hospital he was able to walk from the cab to the ward.

The physical examination showed that he was a rather bony adult, somewhat stuporous, but answered questions fairly well. He wandered at times,

but was not obstreperous, and there was no evidence of paralysis. When he slept the right eye remained partly open.

During his stay in the hospital his temperature remained subnormal, with the exception of September 3d, when it rose to 100.2° F. He showed no evidence of glandular enlargement; his pulse was regular but of low tension. There was a faint systolic murmur heard at the apex of the heart, not transmitted into the axilla; the second pulmonic sound was accentuated. His appetite was poor; the abdomen was apparently normal. The muscular system was poorly developed. Sensation could not be well determined because of the patient's mental condition. There was ptosis of the left upper eyelid. Reflexes were normal. The urine showed a faint trace of albumin. While in the ward he became restless and would get out of bed to wander about; generally, he was quiet and drowsy.

On September 7th he had incontinence of feces for the first time, and on the 9th optic neuritis was first detected. On September 13th Kernig's sign was present, but lumbar puncture gave a negative result. On September 18th Kernig's sign was more marked; the head was considerably retracted, and he had incontinence of urine and feces. There was a conjunctivitis present on the right side, and the patient was noisy and incoherent. On the 21st Kernig's sign was less marked and the abdomen was retracted; there was no paralysis. He died on this day.

Clinical Diagnosis. Meningitis, cerebral tumor.

Autopsy. The autopsy was performed thirteen hours after death by Dr. Adami. The body was that of a long, lanky, middle-aged man, rigid and slightly livid. The left pupil was irregular, as though from some operation; there was a conjunctivitis of the right eye and a slight erosion of the cornea. The chest was long and narrow; abdomen rather sunken. There was a slight pedunculated papilloma on the inner side of the right knee; feet extended, toes retracted. On the inner side of the lower third of the leg was a small pigmented area measuring 3 x 4 cm., there was also slight pigmentation extending up along the inner side of the right thigh; no increased pigmentation of areas normally darker in color.

Head. The skull-cap was easily removed, the dura was not congested, but was a little opaque. When this was removed the right side of the brain was seen to be full and the convolutions slightly flattened.

Brain. Weight, 1435 gms. No adhesions between the dura and pia; superficial vessels moderately congested; the organ symmetrical. Upon examination of the base a suspicious granular appearance was noticed over the anterior and inferior angles of the temporal lobes. On further examination a small broken-down area discharging grumous material was found at about the middle of the second left inferior temporosphenoidal convolution. The microscope revealed in the discharged material diplococci staining by Gram's method. On section the brain showed in various places irregularly scattered pigmented areas varying in size and depth of color; the smaller ones were just about the same color as the cortex, but were more granular in appearance, the larger ones were dark brown, as from old hemorrhage.

These areas were not sharply circumscribed and occurred, for the most part, in the white substance just beneath the cortex. The smaller areas were of firmer consistency than the brain substance, the larger ones were quite friable. There was evidence of slight chronic meningitis about the circle of Willis.

Neck. Pharynx, a few scattered ulcers were found on the right side, with a small amount of pus. Larynx and trachea normal; thyroid well-formed, but a trifle small.

Thorax. Left lung: weight, 565 gms. There were a few firm adhesions at the apex and also along the line of the first rib on the left side; no fluid in pleural cavities. In the apex of the lung was a spiculated calcareous obsolescent tuberculous nodule; otherwise the lung was normal and there was no sign of secondary growth. Right lung: weight, 875 gms. Fairly frequent, small and fibroid obsolescent tubercles were seen in the region of the apex. On the lateral aspect of the upper lobe and about its middle was a firm, roughly spherical mass projecting slightly above the surface. This cut with some resistance and on section had a decidedly cancerous appearance. It measured 3 x 4 x 4 cm. It was mottled with areas of pale brown as from old hemorrhage; a similar but smaller mass was found in the lower lobe near the root of the lung, and one or two miliary nodules of the same nature were found in the substance of the same lobe.

Heart. Weight, 250 gms. The heart was rather small. All the valves, except the mitral, showed fine verrucose vegetations along the lines of apposition of the cusps.

Abdominal Cavity. There were a few translucent lymph cysts in the neighborhood of the head of the pancreas, which could be easily removed from the mesentery.

Stomach, normal; *intestines*, normal.

Liver. Weight, 1352 gms. A small angioma was seen on the surface of the right lobe just above the middle of the anterolateral aspect. The whole organ was slightly congested.

Spleen, normal.

Pancreas, small but apparently normal.

Adrenals. The left adrenal was large and pale and was the seat of several whitish nodules, the largest measuring 11 mm. in diameter. There was another nodule almost the same size, and one that measured 8 mm. in diameter. The right adrenal was larger and contained one large central cancerous mass. Two or three lymph glands in the neighborhood and to the inner side showed a distinct enlargement, and are firm and pale. On the left side in front of the kidney was one firm globular gland which appeared to be partly hemorrhagic, partly cancerous.

Kidneys, normal.

Bladder, normal except for the presence of two small pedunculated polypi.

Anatomical Diagnosis. Chronic basal meningitis; subchronic verrucose valvular endocarditis; ulcerative pharyngitis; ulcer of cornea; primary carcinoma of adrenals, with metastases in the right lung, brain, and peritoneal lymph glands; polypi of bladder; obsolete tuberculosis of both apices.

Microscopic Examination. The tissues had been preserved in Orth's and Zenker's fluids, with the exception of the brain, which had been preserved in formalin. Small pieces of these tissues were treated in the usual way by dehydrating gradually and embedding in celloidin and paraffin. The sections varied in thickness from 3 to 6 μ in paraffin and from 5 to 10 μ in celloidin. These sections were stained with hematoxylin and eosin, thionin, safranin, gentian violet and eosin, Mallory's stain for connective tissue, and by Gram's method in the case of the sections from the lung. They were cleared in xylol or creosote and mounted in Canada balsam. Preparations to show the reticulum were made by Mall's method and stained with nigrosin.

Sections from the kidney, pancreas, and left lung showed no abnormality. There was no sign of new-growth in the heart.

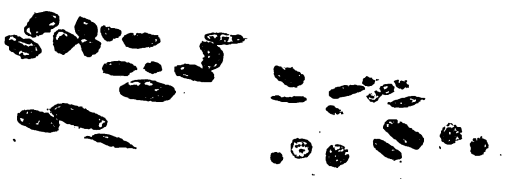
Adrenal. Sections cut through the entire thickness of the gland showed, when viewed with the low power, several nodules of deeply staining tissue, apparently well circumscribed by normal gland substance. One of these nodules was apparently in the fasciculated zone of the gland and was bounded externally by normal glomerulosa, internally by normal medulla, and on the sides by normal fascicularis which above was continuous with the normal zona glomerulosa. When thinner sections of the same nodule were studied with the higher power it was plainly seen that the circumscription was not as well marked as it had seemed upon first examination (Fig. 9). The inner part of the nodule was composed of pure tumor tissue, while its edges were composed of a mixture of this same tissue with normal gland tissue. Upon still closer examination it was readily seen that the transition from true gland to tumor is not abrupt, for in columns of cells—for the most part normal—certain cells were seen that approach the type of cells in the tumor mass (Fig. 1). The cells of the gland were, as usual, rather large cells with perfectly round nuclei; the nuclei relatively palely stained, the protoplasm was either coarsely granular or finely reticulated and stained pink with eosin. As these cells became changed to assume the type of tumor cells, the nuclei became larger and oval, or irregularly shaped, with a deeply staining chromatin network. At the same time the protoplasm took on a rather bluish tinge with the hematoxylin and eosin, and became relatively less in amount.

By such stages a type of cell was produced which was much unlike the normal gland cells, but between these two types all the stages could be followed in a single field of the microscope.

There was one area in the zone of the gland bounding the tumor mass in which the growth had involved the zona glomerulosa. This was apparently not an involvement by simple extension, for there was normal tissue between the large tumor mass and this microscopic one. In this the picture presented was very interesting (Fig. 2), for the whole area was composed of small islands of cells interspersed with other islands of tumor cells which were more nearly of the gland type than of the tumor type. But among the normal cells could be seen occasional transition forms.

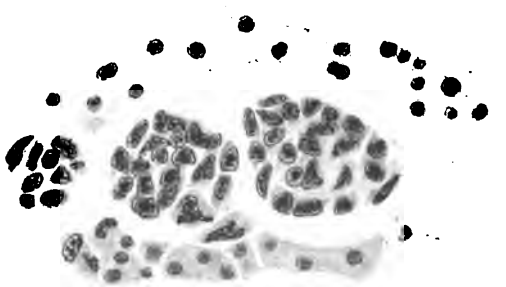
Such appearances, together with the fact that the original tumors are

FIG. 1.



Adrenal. Transition from true gland to tumor. Hematoxylin and eosin. Leitz. Obj. 6, Oc. 5.

FIG. 2.



Adrenal. Transition in the zona glomerulosa. Hematoxylin and eosin. Leitz Obj. 6, Oc. 4.

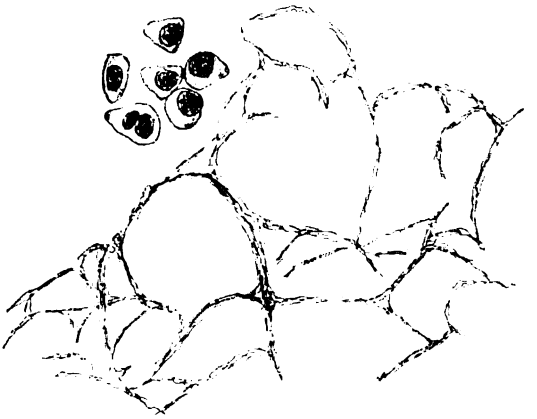
FIG. 3.

Lung. Wall of a bloodvessel. In lumen a couple of strands of tumor cells. (Camera lucida.) Hematoxylin and eosin. Leitz Obj. 6, Oc. 1.

FIG. 4.

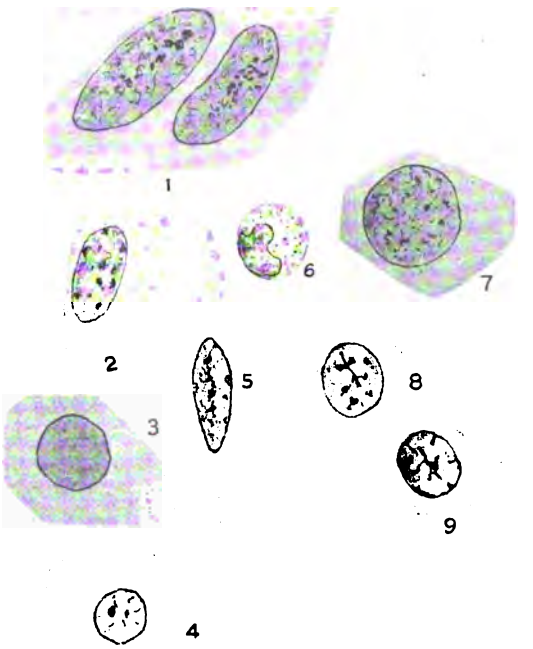
Lung. Wall of bloodvessel showing subendothelial growth with "layer" structure. (Camera lucida.) Hematoxylin and eosin. Leitz Obj. 5, Oc. 1.

FIG. 5.



Reticulum of adrenal tumor, with cells from corresponding section. Hematoxylin and eosin. Leitz Obj. 6, Oc. 1. (Camera.)

FIG. 6.



Cells from tumor and metastases. 2, 3. Adrenal. 1, 5, 7. Lung. 8, 9. Brain. 4. Normal adrenal. 6. Leukocyte. Hematoxylin and eosin. Leitz 1/12, Oc. 4. (Camera.)

bilateral, indicate very plainly, it seems to me, that the growth originated, not in one cell or group of cells which by their growth produced a tumor, but rather in the cells of the glands, which, influenced by some biologic change, lost their physiologic or acquired characteristics, and retained simply their embryonic or formative characteristics.

Then, too, the gradual transition that is seen taking place from normal cells to abnormal tumor cells, completes the evidence of the process.* Cells have not been cut off from their normal relations by fibrous tissue, for the stroma of the tumor is just as much like that of the original gland as it can be, and corresponds well with Flint's pictures of the reticulum. All about the edges of the tumor mass in the adrenal this gradual change can be seen, with no evidence at any place of inclusions.

There was some difference between the cells at the periphery of the nodules and those in the center. In the center they became more elongated, both as to general cell-shape and as to nucleus; their reactions to stains were the same. There were, besides these cells, others with a finely granular protoplasm which showed a very faint violet with thionin; not the pure metachromatosis of the "mastzellen," but approaching it. These occurred between the columns of the tumor cells. The cells of the tumor masses were arranged much like those of the normal fasciculated layer of the gland. At the periphery this arrangement was most complete, in the centre less so. Between the columns were scattered small round cells of formative type with occasional polymorphonuclear leucocytes. Red blood cells were seen in the vessels. There was no evidence of vascular alveolar formation, no evidence of vascular new formation, and no evidence of primary involvement of the connective tissue. Mitotic figures were common, and were regular and irregular in type; multinucleated cells were frequent.

At least the larger part of the supporting tissue was intercolumnar; when a single cell of a small group of cells was surrounded by such tissue it would seem that this was because columns had been cut transversely. A study of the reticulum illustrates this point. By comparing the size of the cells in the sketch of the reticulum (Fig. 5), it will be seen that the meshes of the reticulum are all larger than the largest cells. I am forced, therefore, to conclude that, as in the case of true sarcoma, there is an absence of intercellular network. This conclusion has also been strengthened by carefully staining sections by Mallory's method.

Lung. In the lung, light was shed upon the method of metastasis. Here were very recent growths as well as ones less recent, and the progress of

* It is interesting to observe that Jores, describing the one almost identical case which I find on record, makes a like observation. He states: "Die Stellen aus sich nachweisen lässt, das die Geschwulstzellen aus den Parenchymzellen der Nebenniere direkt hervorgehen, sind es, die dem vorstehenden Fall ein besonders Interesse verleihen. . . . . An manchen Stellen setzten sich die Maschen der Zona fasciculata in das stroma des tumors direkt fort. Die Parenchymzellen der Nebennieren wandelten sich in Geschwulstzellen um. Man sah in einer Alveole noch erhaltene Nebennierenzellen und rundliche Geschwulstzellen nebeneinander liegen. . . . ." (Jores, Deutsch. med. Woch., 1894.)

growth could be readily followed. That metastasis had taken place by the venous system was probable both from the history of other cases of malignant tumors of the adrenals (illustrated by those of Leva,[23] Peacock and Bristowe,[24] Thompson,[26] Dickinson,[39] Affleck and Leith,[43] Eberth,[46] Fox,[49] Rosenstein,[60] and Rolleston and Marks[55]), and from the distribution of the metastatic growths. This evidence was completed by the recognition of tumor cells lying free within the bloodvessels. The nodules in the lung are not, apparently, as well circumscribed as in the adrenals, and on closer study this is seen to be due to the fact that the growth follows the bloodvessels.

There are two possible methods whereby this growth, in such intimate relationship to the vessels, has been produced. The fact that tumor cells were free in the blood might indicate that both had come into play. One method is that which results from thrombosis with tumor cells; the other is that resulting from rupture of a tumor mass into the blood stream with consequent transplantation of the cells into the vessel walls without obvious thrombosis. A study of portions of the tumor nodules revealed evidence of the occurrence of both these processes.

In one section of a lung nodule I encountered a vein cut longitudinally, with a mass projecting into its lumen (Fig. 11). A study of the relationships of this projecting mass showed that the condition was that of a nodule of tumor tissue which had developed on the outer side of the vessel wall, had involved all the coats, and had extended along the vessel wall subendothelially. At one place the endothelium had given way and a few cells were liberated and were to be seen free in the lumen.

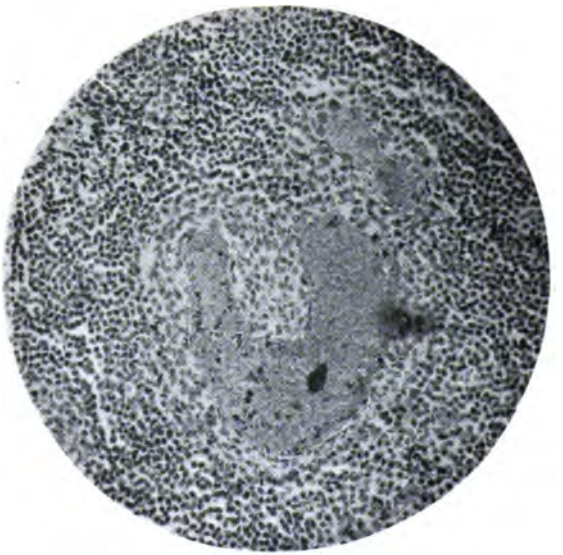
In another section (Fig. 8) the bifurcation of a vessel was seen to be plugged with a mass of tumor cells; this mass had become covered in the muscular surfaces with endothelium, but from this mass the growth was progressing subendothelially. Of course, the fact that a mass of tumor cells is covered by an apparently normal and intact endothelium is no proof that the growth has taken place primarily beneath that endothelium, for, following transplantation of tumor cells upon endothelial surfaces, the endothelium may increase and completely cover the resulting mass and give rise to the appearance of a subendothelial growth. This is well illustrated in the very interesting case reported by Martin,[100] in which transplantation occurred upon the peritoneum and in which the peritoneal tumors were covered by an intact layer of mesothelium. This case of Martin illustrates also the same subendothelial growth in the vessels that is present in my case.

That this appearance was not the result of a slanting cut could be plainly seen in the section. The subendothelial or perithelial growth can be seen in Figs. 3 and 4.

The cells in the lung metastases varied considerably in appearance with the age of the nodules. In the more recent nodules the cells were polyhedral, with the usual large dark nuclei and small amount of cytoplasm. As the nodules grew the type was changed to a more elongated form which in some places became of the real spindle-celled form.

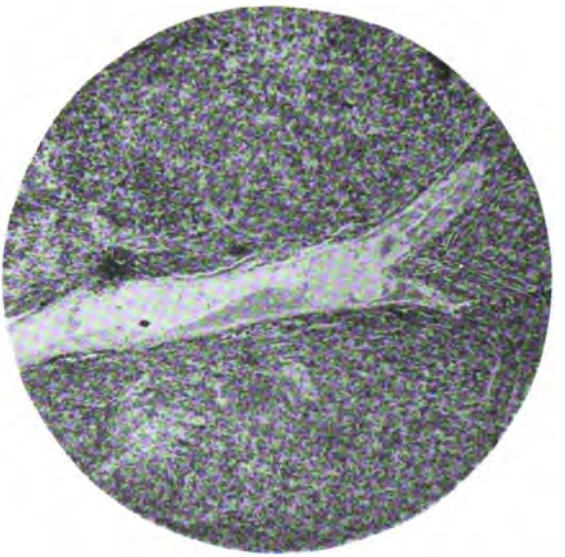
Here, too, was no evidence of active participation of the connective tissue

FIG. 7.



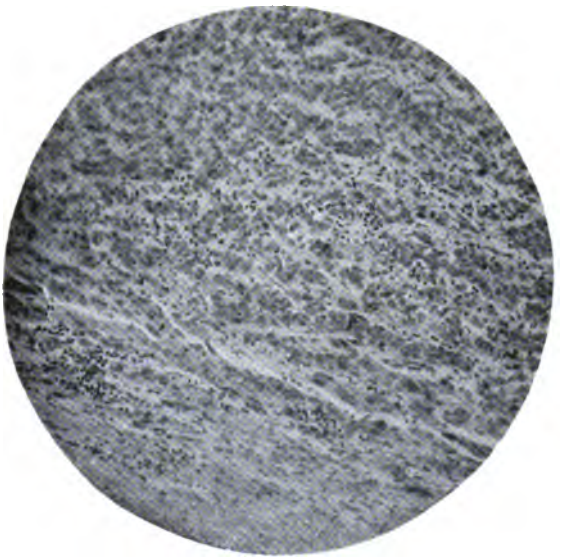
Brain. Intravascular polypus composed of tumor cells covered with intact endothelium and springing from the perithelial subendothelial growth. Photomicrograph.

FIG. 8.



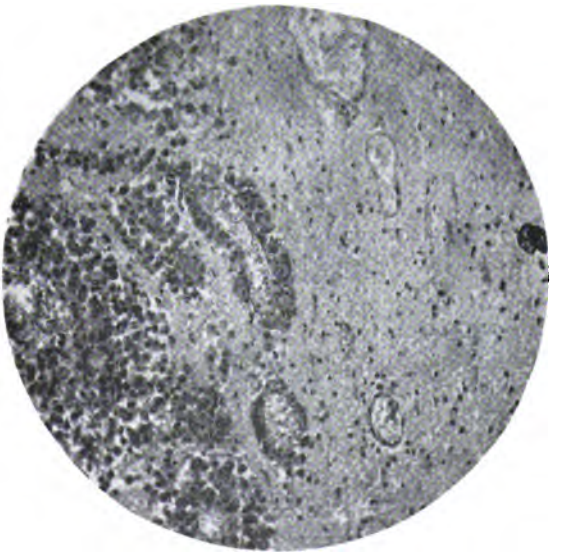
Lung. Thrombosis of a vein with tumor cells showing subendothelial progression. Photomicrograph.

FIG. 9.



Adrenal. Edge of tumor bounded by adrenal gland substance. Photomicrograph.

FIG. 10.



Brain. Early endothelial growth about bloodvessels. Photomicrograph.

or of the muscle of the vessel walls of the endothelium. The most that could be said of the endothelium is that it bounded the growth in the blood vessels. In some of the vessels of the lung there were some micro-organisms of the type of diplococci. These were seen in thionin preparations, but were not stained by Gram's method.

Finally, here, as in the adrenal, were considerable numbers of small round cells scattered throughout the tumor masses, and about these masses there was a certain amount of consolidation of the lung with multitudes of polymorphonuclear leucocytes.

Lymph Gland. Section of the lymph gland from the neighborhood of the adrenal showed an almost complete replacement of the normal gland by abnormal cells of the blunt-spindle type; there was no evidence of any special orderly arrangement.

Brain. Sections of very small nodules showed a marked subendothelial growth (Fig. 10). The distribution here for the most part followed the blood supply, and in all but the smallest vessels an intact endothelium could be plainly seen. No new vessel formation was apparent. In the larger tumors there was much hemorrhage, but the type of tumor was the same, except that especially at the periphery of the growths the vessels could not be seen. In some cases the vessels could be seen to be thrombosed by tumor cells. Another method of vascular obliteration is seen in the brain. At one point, and followed in serial sections, there was a papillary growth into the vessel lumen. This growth was composed of tumor cells of long polyhedral or blunt spindle form and supported by a very delicate supporting network; its surface was covered with normal endothelium (Fig. 7).

The cells in the brain tumor differed still more markedly from the cells of the original tumor than did those in the lung metastases. Here the type was in the greater part that of a small round-celled sarcoma; cells with large dark nuclei and with very little protoplasm; in other words, cells of the markedly proliferative type. Some spindle cells did occur, and these about the vessels in the older nodules. Mitosis was very common.

To indicate the relative sizes and the appearance of the cells characteristic of the unaffected gland tissue and of the primary growth, and the metastases in the lung and brain, I have selected with care typical cells from these regions and drawn them with the camera lucida under the same magnification (Fig. 6). The striking differences in size are easily recognizable.

Here, then, was a tumor originating in the cortex of the adrenal, probably in the fascicular layer, which showed in the primary growths adenomatous and epithelial characters, and in the metastases a somewhat alveolar type of round-celled sarcoma verging toward spindle celled, and subendothelial in location.

Such differences between the primary growths and the metastases are remarkable. There have, of course, been cases reported in which

two types of primary tumors were present.[15] That this is not such a case I have convinced myself after a very careful study of many sections. The metastasis in the lymph gland just at the side of the adrenal gland has a purely sarcomatous type—very different from the appearance of primary growth. Besides, a study of the embryogeny of the adrenal throws a most significant light on the subject, and, it seems to me, explains the apparent anomaly.

It is true that there have been many differences of opinion existing among the embryologists on the subject of the origin of the adrenal bodies, but now the subject seems to have been settled. Flint,[13] in his monograph, epitomizes the subject up to 1900. Since then a very valuable paper has been published by Aichel,[70] who makes a very careful study of the adrenal from the standpoint of comparative embryology, with the result that he has described both in words and by drawings the complete series of the steps in the development of the adrenals from the lower vertebrates to man.

The old idea was that the adrenal was composed of a mesoblastic part which corresponds to the adult cortex of the gland, and an epiblastic part, corresponding to the medulla. This view has been the prevalent one up to quite recently, and it was elaborated and substantiated by Balfour, Mitsukuri, and Inaba. Janosik and Gottschau, however, held that the cortex was mesoblastic and that the medulla was in turn derived from the cortex, and these authors' views were accepted by Minot.

Flint[13] makes some interesting observations which are but modifications of those of Minot, Janosik and Gottschau. He says: "The cortex of the medulla* (gland) is first formed and then the medulla appears as small groups of cells beneath the capsule, which begin to grow into the cortex. They begin their migration in (pig) embryos from 6 to 8 cm. long, and reach the central vein when the embryo is between 12 and 15 cm. in length. When this point is reached there is a gradual increase in complexity of both cortex and medulla until the adult structure is reached."

As he says, also, that islands of medullary cells may remain in the cortex, it is plain that there is a chance for cortical tumors to be medullary in origin. (That this is not the case in the present tumor

* The use of "medulla" here is evidently not intentional, and due probably to an oversight. By the context it is very plain that Flint means "the cortex of the gland."

is beyond doubt, for all the changes can be traced with little or no difficulty to true cortical substance.)

The only difference between this view of the origin of the medulla of the organ and that of Minot, Janosik and Gottschau is that these observers hold that the medulla is derived from internal layers of the cortex.

Aichel discusses the question of the genesis of the adrenal in a very thorough manner. This author studied the matter from the standpoint of comparative embryology with most gratifying results—gratifying in this, that he was able to obtain parallel and concordant observations from the lowest to the highest forms of vertebrates. He comes to the conclusion that the interrenal bodies of the lower vertebrates correspond to the adrenals of the higher vertebrates, and that both arise from the "urniertrichter,"* and the "urniertrichter" is of mesothelial origin, to employ Minot's term. The "Marchand's adrenals," or the supernumerary adrenals found in the broad ligament of the female and near the prostate and spermatic cord in the male are, he found, derived from the segmental tubules of the Wolffian body, and correspond, therefore, to the suprarenals in the lower vertebrates.

The other adrenal tissue, such as occurs in the right lobe of the liver and in the kidney and in the adrenal itself, may be true adrenal tissue that has been separated from the rest of the anlage. That cortex and medulla arise from the same Wolffian body cells, he states confidently, and his account reads very much like that of Flint.

It appears, then, that, dismissing the older view of Balfour, Mitsukuri, and Inaba, the adrenal bodies are primarily of mesothelial origin. By using "mesothelial" rather than "mesodermal," I mean that the gland in its adult form is a derivative of that portion of the mesoblast which later comes to line the body cavities—*i. e.*, pleura, pericardium, and peritoneum, and the cavities formed from peritoneum. A review of the main facts of the history of the genesis of the embryonic layers may assist in a better understanding of the facts before us.

From the one-cell stage the ovum proceeds, after fertilization, to the multicellular stage. At an early period these cells form a single

* Aichel's illustrations show very well what he means by "Urniertrichter," or "Wolffian body funnels."

layer, which later multiplies to form two layers, the "ectoderm" and "entoderm." Later still, between entoderm and ectoderm there appear certain cells which are the primitive elements of "mesoderm." These latter are gradually differentiated into two groups, part of them, the group nearest the medullary groove—the mesenchymal anlage—remain as a mass, from which later the connective tissues are derived, together with possibly the blood and bloodvessels and the spleen; those farthest from the medullary groove become separated into layers, and the superficial cells of the splanchnopleuric and somatopleuric mesoblast, the lining cells of the primitive body-cavity, give rise in later stages to the serous membranes, the urogenital tract (except the bladder), and striated muscle. So it is seen that with a common origin the mesothelial element becomes more highly differentiated than the mesenchymal, and acquires in a certain degree the so-called "epithelial" characters; by which is meant that the cells are more or less independent of a direct blood supply, that they are covering cells and that they have no true supporting membrane, but are united by a simple undifferentiated cement substance.

It is also plainly evident that if the laws of specificity of the germ layers hold good in the reversion of the mesenchymal tissue, it will be easier for it to revert to the primary mesodermal type than it will be for a mesothelial one to do the same, but that mesothelium in spite of its acquired epithelial characters may ultimately in its reversion become in type that of mesoderm.

If we start with the two propositions, first, that the characters of neoplastic cells are not of the nature of new acquirements, but on the contrary are reversionary; and second, that characters most recently acquired are those which are first lost (as Virchow has intimated), and those first acquired are the last to be replaced, then we may say, that, although all tissues of the body are derived from a single cell whose progeny have become differentiated more and more, yet all tissues will not revert with equal ease to the stage of completely undifferentiated cellular structure, and that structures of epiblastic and hypoblastic origin will retain their lining membrane characteristics with greater tenacity than those of mesoblastic origin, whose lining membrane characters have been assumed at a later date, even after previous differentiation in the original middle layers of the embryo. In other words, mesothelial tissues in assuming regressive and prolifera-

tive peculiarities will more readily lose their epithelial qualities than will epiblastic or hypoblastic tissues and sooner and more easily reach the primitive morula type. And for the same reason we may believe that cells of mesenchymal origin will reach the primitive type more easily than will mesothelium. And so it is comprehensible that tumors of mesothelial origin, while they may retain epithelioid properties, may also manifest all the appearances of true sarcomata. As Jores states, "Ferner kann man nicht gerung betonen, das Sarkome des Nebennieren häufig einen den Carcinomen überaus ähnlich Bau zeigen." (Jores, *loc. cit.*)

It is upon these grounds that the variations in the tumors of testis, ovary, kidney, and suprarenal, all organs of mesothelial origin, can be most logically explained. But these appearances make it plain that our nomenclature for these tumors, as well as our conception of their relationships, must be materially modified.

It is apparent that, embryogenetically speaking, cancer of the urogenital tract is impossible except in the bladder—if that is a term employed only to denote atypical tumors of epiblastic or hypoblastic origin—that all malignant tumors of this tract must be sarcomata; if, that is, we accept this definition that atypical tumors of mesoblastic origin are sarcomata. This use of terms leads us into such difficulties that it would seem wise in the case of the mesodermal tumors, at least, to break away from the traditional terms "sarcomata" and "carcinomata," which are only confusing, no matter upon what basis the nomenclature rests. A good example of the confusion is the case of the tumor described in this paper. If we call it carcinoma we must do so on purely morphologic grounds; and what shall we say of the metastases? They are sarcomata on the same grounds. If we call it sarcoma, it must be on purely embryologic grounds, and it certainly does not look like the sarcoma, even though it be such, logically. But confusion is also caused here by the absence of correlation between the old nomenclature and the morphologic appearances of tissues. Grawitz, Horn, and Sudeck call tumors of adrenal rests carcinoma or sarcoma, a nomenclature which evidently depends upon appearances. Speaking narrowly, malignant tumors of the adrenal can be nothing but sarcomata. Rolleston and Marks[35] state this very well when they say: "Our own impression is that malignant tumors of the suprarenal bodies are peculiar and form a special class. They

may approach structurally either the carcinomata or the sarcomata, and sometimes one and the same tumor may in different parts resemble both."

Since the suprarenal bodies may be regarded as mesoblastic from a developmental point of view, and as epithelial from the morphologic, it is perhaps natural that it is not always easy to assign the tumors that arise in them to either the mesoblastic (sarcomatous) or epithelial (carcinomatous) group of tumors. It is conceivable then that many, though not necessarily all, of the sarcomata arising in the suprarenal bodies are, like carcinoma, derived from the proliferation of secreting cells of that organ.

It seems wise, therefore, to call this tumor a "mesothelioma," following the example of Buxton[96] and the timely suggestion of Minot, that we call serous membranes and their derivatives mesothelium, and also following the suggestions of Adami in his work on classification.* The application of these observations to the tumors of the adrenal gland sheds a very significant light on pathologic processes, and the relationship of embryology and pathology becomes closer, as Minot[1] desires it shall.

When cells in their development gradually lose their embryonic characters to take on more complex ones, their spheres of activity are gradually narrowed, until in the final stage of development there is but one permanent character which remains, and while the cell is functioning normally it cannot do less than carry on its physiologic work. The neuron is the type of this highest stage of development; if it stops it dies; it cannot reproduce. Other cells less highly differentiated have left to them some part of their embryonic characters, and, according to their position, more or less of it. To accomplish their physiologic labor they must be able to reproduce, but while reproduction goes on the more complex function declines to be renewed when reproduction has ceased. When growth and reproduction are at their maximum physiologic function is lost. In other words, the cell has reverted toward the embryonic type, has degenerated, to speak broadly; or, as Adami[7,8] urges, has assumed vegetation and proliferation in place of functional characters.

This reversion toward the embryonic type is what happens in

* An address soon to be published in the Journal of Pathology.

tumor formation, and which culminates in the malignant tumors. In the benign tumors the specific function of the cells is overbalanced by the embryologic one; in the malignant tumors it is lost.

Now, it is true, probably, that "progress and differentiation act as a progressive restriction of further development. Each successive stage of differentiation puts a narrower limitation upon the possibilities to further advance. Applied to pathology the law means that the range of possible pathologic changes is determined not merely by the nature or kind, but also by the stage or degree of the previous differentiation of the tissue (Minot)." And further, the law means that "when cells revert to the embryonic condition, as so often happens in pathologic processes, they never attain such a degree of prematurity that subsequent differentiation is possible with other functions (Le Conte)." (There are some apparent exceptions.)

So we have in the development of cells a limitation in the differentiation, progressive and regressive. Ectothelium never becomes more or less than ectothelium, and the same is true of the other tissues. The only difference lies in the fact that the most variously differentiated tissue may show more various features in reversion, as is true in tissues of mesodermal origin.

We can now see that the changes in the tumor described above are in harmony with the laws of histogenesis. Such a series of changes as has been depicted indorses and emphasizes the results of embryologic study of the adrenal bodies. Cells that undergo such changes can have but one origin according to this law, they must be mesothelial. So, as Minot says, "It is more than probable that all pathologic tissue is as strictly governed by the law of specific value of the germ layers as are normal tissues." This law holds in reversion as in development.

This state of affairs is voiced by Lubarsch[64] in the following words: "So bald eine Zelle biologisch als Epithel- oder Bindegewebszelle in weitesten Sinne differenzirt, kann aus ihr nur noch eine gleichartige Zelle werden."

It will suffice, I think, at this time to remark that, in looking over the literature for primary carcinomatoid tumors of the adrenals, and subjecting the reports to the criteria laid down by Rolleston and Marks,[35] I have been able to find twenty-one cases besides my own. At a later date I shall collect my notes and publish them. For the present I will simply state that the cases I have selected, which were

well-described microscopically and which showed metastases, are those of Fenwick,[35] Brooks[36] (two cases), Carriere and Delearde,[42] Pawlick,[17] Rolleston and Marks[35] (three cases), Ogle,[23] Ritchie and Bruce,[25] Weinburg and Turguet,[40] Brüchnow[18] (three cases), Orth[94] (two cases), Marchand,[95] Collinet,[19] Stoukoventoff,[71] Possett,[96] and Hansmann.[21]

CONCLUSIONS—SUMMARY.

1. Carcinomatoid tumors of the adrenals are rather uncommon, only twenty-one cases being on record.

2. The application of the terms "carcinoma" and "sarcoma" to tumors of mesothelial origin is misleading, and may be discontinued with benefit. The term "mesothelioma" is a better term.

3. Regressive changes in neoplastic tissues correspond to relative losses of physiologic function and relative gains in formative characters.

4. Tumors of mesothelial origin may vary in type in their primary growths and in their metastases, and these variations are evidences, in reversion, of the various stages in the genesis of the tissue in which the tumors originate.

5. The tumor described above is a malignant mesothelioma of epithelial type (mesothelioma malignum carcinomatoide).

I desire now to thank Dr. Adami for his gracious kindness and ever-present encouragement to me in my work.

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A FURTHER CONTRIBUTION TO THE SUBJECT OF VASOMOTOR ATAXIA.

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THIS communication is intended to supplement the articles published in the *Philadelphia Polyclinic*, June, 1892, and the *American Journal of the Medical Sciences*, February, 1894. While in the description of his cases no other writer has adopted the term "vasomotor ataxia" proposed in the communications referred to, yet a number of cases belonging to one or another subgroup of this general class have within the last few years been placed upon record under other names, new or old. Reference may be made especially to the phenomena of vascular throbbing in certain neurasthenic patients (angiopathic neurasthenia), described by Dana in 1897, and to Savill's[1] discussion of the neurovascular disorders of the extremities. In brief, the class of cases to which it is desired to recall attention exhibit multiple and diverse phenomena suggestive of instability of vasomotor control, central and peripheral. To cite but a few examples: In one subject a slight blow upon the skin will produce circumscript edema, or even extravasation; in another a slight indiscretion in diet will be followed by swelling of one side of the face and lips; in another, without traceable cause, "blood blisters" will appear in the pharynx. One will suffer to-day with urticaria, and next week with asthma; another will have paroxysms of migrain alternating with gastric crises, and sometimes attended with mucous enteritis; one will manifest acroasphyxia with mild vertiginous phenomena; another may have no marked symptom except hay fever in its due season. In no person are all the phenomena invariable; in few is there but a single group of manifestations; in none are the exciting causes always definite and the same; but in all certain stigmata of the condition are constantly present, and upon

[1] On Acroparesthesia, Erythromelalgia, Sclerodactylia, and other Angioneurotic Disturbances, with an Attempted Classification of Angioneurotic Disorders of the Extremities.—*The Lancet*, June 1, 1901.

their recognition depends the diagnosis—which consists in the assignment of the individual to his class, rather than in the giving of a name to the special symptoms presented at a particular moment.

I shall not detain the Association with reports of cases, of which I have gathered very many. A sufficient number is already on record to illustrate nearly all the points to be touched upon, while so great and so varied are the number and character of the symptoms manifested in individual patients at one time or another, that their recital would leave no time for the main purpose of the present communication. I shall ask attention rather to certain considerations pertaining to the philosophy of medicine, and especially to that portion thereof that an eminent English observer has denominated the study of "the synthesis of disease."

In studying the aberrations of the human organism we must take into account not only the forces of the environment that may excite disturbance, but also the forces within the body, through derangement or failure of which the disturbance becomes manifest. In so doing, we have to consider not only chemical and physical action and reaction, not merely cells, tissues, organs, systems and functions individually, but also—to adapt Whewell's term—the "consilience" of the organism.

That there are differences in the responses not only of different species, but also of different individuals of the same species, to environmental changes, is a matter of every-day observation. The same order of facts obtains likewise in the pathologic laboratory, and may be manifested even when the species is one so little resistant to infection as the guinea-pig, and the environmental change one so decided as the inoculation of cultures of tubercle bacilli. A certain child may swallow several grains of a quinin salt and exhibit no obvious disturbance of physiologic equilibrium; another takes but a fraction of a grain and becomes febrile, flushed and delirious. Of several men exposed to the same cold winds and snow, one contracts pneumonia, one exhibits hemoglobinuria, another suffers with frost-bite, another manifests Raynaud's phenomena in the extremities, and some escape with slight discomfort.

In a case under my own observation, a boy, aged seven years, was so markedly affected by two grains of cinchonidin salicylate, administered by his mother, that, until I had learned of the drug-giving, I suspected the existence of scarlatina. A woman, aged forty years,

exhibited general anasarca following the administration of strychnin, of nux vomica, of picrotoxin—the two latter agents being given as tests of the susceptibility. A woman, aged twenty years, went into a cataleptic state of nearly two days' duration following the use of one-eighth grain of morphin sulphate by the mouth; after recovering she informed me that a similar condition had occurred in sequence to the hypodermic use of morphin some years previously. She did not know that my prescription contained morphin. All these patients possess in some degree the physical and psychic characteristics to be described later.

It is quite easy to speak of peculiar individual responses to drug action, to bacterial attack, to meteorologic conditions, to psychic influences, as "idiosyncrasy;" but is this not merely another form of the ostrich-like head-hiding habit that is too common in professions having a technical terminology? What shall it profit us to translate our ignorance into Greek? Idiosyncrasies must have a physiologic basis; normal as to the individual, they are abnormal as to the race. In certain instances, undoubtedly, they are but manifestations of that tendency to variation, of which evolution sometimes takes advantage to improve the species; in others they are of a more general character. When such an apparent abnormity is congenital, usually inherited, often shared with others of the same family—and in addition is manifested by members of many unrelated families—it is evidently not so purely individual as the term idiosyncrasy would imply; but is representative of a condition actually or potentially present at some time in all men. It is abnormal not *quoad naturam*, but *quoad tempus*. It may be a reversion to a condition formerly common to the race, or may be the beginning of a new development of good or evil promise.

I am not unmindful of the fact that modern tendencies are toward the discrimination and separation of syndrome groups through specific etiologic, morphologic, and metabolic characteristics, rather than toward their inclusion in general classes through broad functional relationships. We seek for definite responses to definite irritants as criteria for the new nosology that shall substitute accurate description for vague surmise. Even the rather definite group of cases that we now include under the term of typhoid fever will doubtless be divided into several other groups, differentiated by data of gross or minute pathologic anatomy and of bacteriology; acute polyarthritis no longer

means rheumatism; hematology is rapidly accumulating the basic facts for a reclassification of the anemias. It may thus at first view appear retrogressive to erect a nosologic class based upon the very indefiniteness of the exciting causes and the organic responses; and including syndrome groups apparently so opposite as those to which the names of Graves and of Raynaud have respectively been given. The endeavor to determine the exact nature and location of the metabolic and histologic alterations that are associated with these syndromes would seem much better worthy of attention. Of the great importance of minute and exact research there can be no question, but upon the interpretation of its results there may be division of opinion. That opinion is not unanimous concerning the etiology or pathology of Raynaud's disease, or of Graves' disease, may have other explanation than incompleteness of research. The great biologic question as to the relation of structure and function is here involved. If function may precede and determine structure in normal evolution, a similar sequence may take place in pathologic evolution. The morbid alterations discovered after death in bodies that during life have manifested the functional disturbances described by Graves or by Raynaud may be, in greater degree than we believe, sequential rather than precedent.

By the term vasomotor inco-ordination, or ataxia, it is proposed to designate not a disease, but a fundamental disorder, out of which, through the incidence of varying exciting causes, varying syndrome groups may be developed. If the eternal question, "What is the explanation of that explanation?" may still be asked, and must for the present remain unanswered, nothing in medicine or other sciences is free from the same limitation. The fundamental disorder to which reference is made is a deficiency, rather than a perversion of the normal order. It may be congenital or acquired; in the former instance manifesting incomplete development, individual, familial, or racial; in the latter instance illustrating Hughlings Jackson's law—which is but one aspect of an universal law—that neural functions latest developed are earliest overthrown. The function in question is that of inhibition of cardiovascular motion. As heart and vessels have been developed from one primitive tube, and their nerve-supply has arisen from one primitive source, it is convenient to speak of vasomotor—meaning cardiovasomotor—phenomena. The importance of inhibition

in evolution, biologic and sociologic, may briefly be alluded to. Life, development, progress, depend upon it. The inhibition of chemical and physical changes occurring under ordinary environmental conditions, so that response to certain definite environmental stimuli may become more and more specialized—even seemingly purposive—is one of the principal distinctions between living and non-living matter, and, in progressive degree, between various kinds of living matter. The inhibition of psychic responses of a kind unfavorable to mental and moral progress influences the development of individuals and races. The inhibition of individual desires and tendencies by the forces of organized society makes civilization possible. This is one side of the shield, of which the other is termed voluntary activity or will. In other words, the evolution of inanimate matter into bioplasm, of bioplasm into men, of men into civilized communities, is characterized, first, by gradually increasing control of the reactions of the organism to the forces of the environment, and, second, by progressive organization of this control, so that what was at first volitional, or, at least, the result of effort accompanied with consciousness, becomes automatic. This automatic control, or inhibition, is not annulment of the function restrained, but regulation—preservation of normal balance—and thus involves also the excitation of the function under appropriate conditions; the pneumogastric inhibition of the heart being the clearest example. The normal balance of cardiac function being represented by a rate of seventy-two beats to the minute in the quiescent man, normal pneumogastric control permits acceleration of the cardiac rate within certain limits, to meet the demands of exercise, in resisting the attacks of certain pathogenetic agents, in the attempt to compensate for structural or functional perversions in the blood or in the heart itself, and under other conditions. One of the lower animals, being frightened by the approach of an enemy, seeks escape in flight. The normal mechanism of his flight calls for relaxation of pneumogastric restraint; the heart beats rapidly, the eyeballs protrude, it is possible that the thyroid gland may enlarge with the increased supply of blood. The tendency to this association of phenomena under fear and certain other strong emotions that find vent in muscular activity, is an evolutionary inheritance among human beings also. I have observed in human beings protrusion of the eyes sufficient to show the sclera above and below the cornea under certain conditions of

emotional excitement accompanied by increased cardiac activity; notably in a nymphomaniac, but in less degrees in others, both men and women, in conditions of non-sexual excitation. It is, I think, not uncommon in those who at the same time become red in the face from rage. The relation between menstruation and changes in the size of the thyroid gland—especially when the latter is enlarged—is as well known as the Roman matron's custom of measuring the neck of her newly-wedded daughter. But the rapidity of the heart, the protrusion of the eyes, the possible enlargement of the thyroid, normal under certain conditions and subsiding when the occasion has passed, are abnormal under other conditions or if persistent. The woman who, being alarmed, does not try to run away, has no physiologic need for the increased circulatory and nervous activity that helps the frightened rabbit to escape. To preserve the balance of function that we call health, her pneumogastric or other inhibitory activity must be strengthened rather than relaxed under the strain. If it can meet the emergency, there is, perhaps, a transient excitation of the heart, with pallor or flushing of countenance, and then equilibrium is restored; but if not, Graves's syndrome may be initiated, and persist. I have observed at least two instances in women in which the development of persistent tachycardia and goiter immediately following fright, with subsequent development of exophthalmos, seemed to be established beyond question. In other apparent instances of the same kind previous observation had not been sufficiently accurate to exclude the probability of error in date of origin of symptoms. But such is not the history of every case of Graves's disease, nor is such the result of every severe fright to woman or man. Evidently, then, two elements enter into consideration—the one fundamental, the other accidental. The former must be present; the latter may or may not be brought to act upon it. Without the fundamental disorder the exciting cause does not produce the specific result. Without an adequate exciting cause the fundamental disorder does not become manifest in the specific manner. The fundamental condition is one; exciting causes may be various. Various exciting causes having certain features in common may be followed by identical results; as the mechanism of a clock acts in the same manner, whether the pendulum be started by a push with the hand or by the attraction of a magnet. Other exciting causes lead to results resembling those of the first class in some particulars and differing in others. Exciting

causes differ in degree and in persistence as well as in kind; the degree of the fundamental disorder differs in different individuals. Thus the possibilities of diverse combinations of factors being great, the possibilities of results diverse in degree, in persistence, and in individual particulars are equally great; but withal there must be a fundamental resemblance in results, dependent upon the identity of the fundamental disorder. Considering the continual demands of normal function upon the vasomotor taxic mechanism for accurate adjustment to the instant needs of organs, tissues, cells, as well as to the constant demand of the organism as a whole; taking into account, further, the varying conditions of the environment and the necessity for quick response of the vascular mechanism to the necessities of occasion; realizing even then very imperfectly how mobile, yet how steady, must be the vasomotor control—it is not difficult to understand either the importance of this control or the numerous symptoms to which defect therein may give origin.

Granting such fundamental defect, not only do the diverse manifestations described as the basis for this paper become understandable, but also we are able to recognize the origin of many symptoms, otherwise confusing, that may occur in certain individuals during the course of various acute and chronic diseases, and which, without this clue, might lead to serious error in diagnosis or in treatment.

As a matter of fact it is not probable that any individual has complete automatic vasomotor control; yet, equally as a matter of fact, the vast majority of human beings have control practically adequate to all ordinary occasions. The symptoms occasioned by defective control, or, as I wish to term it, *vasomotor ataxia*, are, on the whole, phenomena perfectly normal under adequate causation. Their abnormity lies in the fact of their occurrence under stimuli normally inadequate, in their undue persistence, or in their excessive degree. They are also characterized by a certain associative character, as in the definite syndromes of Graves and Raynaud; the number and character of the associated symptoms depending on factors and relationships that we need not now inquire into. They differ very much in degree, and in character may be either apparently spastic or apparently paretic; that is to say, may indicate either excessive vascular relaxation or excessive vascular constriction. Until the question of dilator and constrictor nerves of the vessels is settled, it

cannot be said that relaxation is actually paretic; in all probability it is at times active. Rarely are all the phenomena in a given seizure dilative or constrictive; both sets of symptoms are often commingled, though one or the other will usually predominate. An individual will, as a rule, show the predominance of the same class of symptoms in his various paroxysms—for example, always becoming pallid or always flushing with his migrainous or vertiginous attacks; though there are many exceptions even to this rule. The flushings, chilliness and other vasomotor disturbances of the climacteric in women are of the same order of phenomena, and, as frequent concomitants of a physiologic process, may be said to be normal. It is to be noted, however, that the process in question is one of devolution.

Individuals of deficient vasomotor control always present certain phenomena indicative of their condition. Some of these stigmata are to be discovered only upon careful search, others may be seen at once; but they rarely attract the interested attention of patient or physician until more marked manifestations occur. The symptoms which lead to the discovery of the condition are, as a rule, paroxysmal in character, and do not recur regularly—or even in an invariable manner, until some special association, as Raynaud's syndrome or Graves's syndrome, becomes, as it were, organized. Among the more or less constant characteristics of those whom I am accustomed to term "vasomotor ataxics" may be mentioned the following:

1. Dermographism can always be demonstrated, and in marked cases factitious urticaria is produced readily.

2. There is usually a tendency, especially during conversation of an exciting character, to contraction of the upper eyelid, exposing the sclera above the cornea. Sometimes this can be developed by having the subject fix his eyes upon a point at the normal level of the pupil, and telling him to open his eyes as widely as possible. I have looked upon it as a larval condition of the palpebral contraction known as Stellwag's sign of exophthalmic goiter.

3. There is in many cases an exaggerated tendency to blushing. Sometimes what might almost be termed a "permanent blush" occupies one cheek or a portion of a cheek. Frequently there will be a tendency for one cheek and one ear to become hot and flushed, without special emotional or other excitation, while the other cheek and ear remain normal.

4. Minute cutaneous angiomata are often to be found upon various portions of the body.

5. The nails exhibit the most constant and definite characteristics. Apart from striations, which are not rare, they show certain strata of more or less definite coloration. In the most pronounced cases I have been in the habit of terming them—in order to impress the condition upon students—"patriotic nails;" the markings being red, white, and blue circular segments. At its base, for probably half its length, the nail is more or less cyanotic—blue, purple, or faintly violet; beyond this there is a broad, whitish area, and then toward the finger-tip the nail becomes pink or red. In the midst of the pink area there appears a semicircular or crescentic line of deep red. Sometimes these crescentic markings of red, white, and blue alternate in greater number. Sometimes there is a blue or white area beyond the deep red line. Sometimes the nail is pink, purple, or leaden throughout, except for red and white crescentic areas toward the finger-tip. At times the skin around the base of the nail is of a deep brick-red color. Usually the nails are curved both longitudinally and horizontally, but sometimes they are flattened. Often there are certain permanent characteristic but indefinite colorings of the fingers, and, at times, of the whole hand. These become accentuated temporarily under conditions of temperature variation, natural or artificial. In certain persons the hands are always more or less pinkish, and the color extends in some instances a greater or less distance up the wrist. In others, the wrist and the palm and dorsum of the hands may be cyanotic, and the fingers pink or pinkish purple. In others, the fingers may be pink or purple, or of mixed hues, and the palms and dorsum of ordinary color. In some subjects there is an irregular mottling. I have noticed this mottling, extending over the arms, or, indeed, over nearly the whole cutaneous surface, as an hereditary phenomenon—and in some cases as a paroxysmal one. In one marked instance in my clinic, red, white and blue areas scattered over the whole body, including the foreskin, developed under observation after the patient—a boy just reaching puberty—had been stripped for examination on a somewhat cold day. Weather changes cause considerable difference in these appearances, cold having a tendency, as a rule, to increase the depth of the cyanotic (venous) hue, while heat tends to increase the proportion of the pink or red (capillary) tint; though this may vary in

different individuals. As a rule, if one hand be kept in ice-water for several minutes it will become red, while the other becomes more deeply blue. Warm water or hot water will redden the immersed hand without obviously affecting the other. Pressure, or stroking, quickly changes the color of the part manipulated to white, but the original coloration returns after a brief interval. Elevation of the hand will cause the color, whether pink, or blue, or purple, to disappear as the vessels become emptied, leaving the hand abnormally white. If the whitened hand then be allowed to fall it first becomes pink at the finger-tips, the pink tint spreading over the hand as the capillaries fill; and then, as the dilated veins begin to receive blood, the coloration will change through various shades to that formerly manifested—the same distribution of blue and pink as in the other hand being observed after some two or three minutes. If, however, the wrist be constricted by a broad ligature when the hand is allowed to fall, the return of the coloration is delayed, or even prevented entirely while the bandage is in place. Even in those who fail to show marked color-changes, slight pressure with the finger-tips on almost any portion of the cutaneous surface will leave a white imprint with red borders persisting for several seconds.

6. In addition to the effect of weather upon the hands, referred to in the preceding paragraph, persons of deficient vasomotor co-ordination usually exhibit marked general sensitiveness to changes of temperature. They may be divided, according to the nature of this temperature reaction, into several groups, of which three may be taken as types. In the first group may be placed those who suffer in summer, but are comparatively comfortable in winter. These will complain of the heat of an apartment whose temperature is pleasant to its other inmates. They sweat excessively on slight exertion, and usually exhibit Shakspeare's "moist palm of youth," even when advanced in years. In such subjects, too, one is likely to find some degree of enlargement of the thyroid gland, and they are always made worse by the administration of thyroid extract. In the second group are those who complain in winter and are usually comfortable in summer. These persons ask for windows to be closed when others in the room prefer to have the windows open. They wish fires to be lighted earlier in the fall than is necessary for the comfort of other people; they usually burden themselves with excessive weight of cloth-

ing; they have dry palms, and even when the weather is but moderately cool their hands may be cold and cyanotic, perhaps swollen, while their noses become either red or white and cold. In some, perspiration is deficient, even in the summer, and these suffer inordinate distress in hot weather as well as in moderately cold weather. Others perspire with undue readiness. The third group includes those who are comfortable only in moderate temperatures, being distressed not only by extremes of summer or winter weather, but even by slight degrees of either heat or cold. In addition, there are numerous individual variations even among those falling into one or the other of these three classes. It is because of these intermediate variant cases that we are enabled to gather all these persons into one class. It will be observed that those who suffer from heat approach to the type of Graves's phenomena, while those who suffer from cold approach to the type of Raynaud's phenomena; yet the vascular phenomena observed in the hands, even among those who show the cyanotic coloration, are not those of excessive constriction of vessels, but of dilatation, as is proved by the experiment of elevation and depression, both with and without ligature, as detailed in the preceding paragraph. Constrictive phenomena of both cyanosis and pallor may occur paroxysmally without obvious cause, or under natural or artificial excitation of sufficient degree.

7. In certain patients, especially those with more or less constant red flushing of the face, if a silver probe be drawn across the flushed cheek a bluish-black mark will be left, which can afterward be wiped off. I assume that this is due to the formation of silver sulphid, but I have not as yet been able to have a chemical study made.

8. Refractive errors are almost invariably present; in the great preponderance of cases there is hyperopic astigmatism.

9. The majority of those who manifest these stigmata would unhesitatingly be classed as "nervous," "neurotic," sometimes even as "hysteric" individuals; yet some whom I have studied are persons of great intelligence and stability of character. These have usually possessed highly developed sympathy and imagination; among them are artists, actors, authors, jurists and physicians of the first rank.

The phenomena just described are more or less constant, and some of them at least will be found in every individual of the class under discussion. Other characteristic phenomena are found in certain individuals only, but in many persons, and in more or less intimate but

inconstant association. Among these, special mention may be made of tingling and numbness—not only in the extremities, but in the face, in the tongue and lips, and sometimes over one-half of the body—and of blood losses—as epistaxis, hemoptysis, hematemesis, hematuria (which may be so slight, however, as to be merely discoverable by the presence of erythrocytes in unusual quantity upon microscopic examination of the urine), hemoglobinuria, retinal hemorrhage, petechiæ, etc. Slight, transient, but recurrent, albuminuria, is not uncommon. Hives and attacks resembling erythema nodosum are manifested with more or less frequency, while recurrent circumscript edema (angioneurotic edema)—sometimes affecting especially one-half of the tongue—or giant urticaria, local or general, may appear in apparent sequence to trauma, to emotion, to indigestion, to food and drug intoxication, or to sudden chill, etc. In some persons the hands will swell to almost twice their normal size when exposed to cold, even in slight degree. These subjects sometimes have attacks of chromidrosis or hemidrosis. Many persons have at different times what may be termed substitutive crises—as vertigo, migrain, asthma, or nausea and emesis.—But to extend the list of symptoms and syndromes would be to begin the record of cases and to pass beyond the purpose of this paper. That the paroxysms or crises are often precipitated by toxic influences of endogenous or ectogenous origin is probably true, but whatever be the toxico-pathologic mechanism of individual symptoms or of special groups of symptoms, underlying all is the fundamental defect of inhibition, which Savill terms "vasomotor inco-ordination," and for which I prefer my original term—vasomotor ataxia.

Apart from the general relationships discussed, there is a practical clinical value to these observations. It lies in the recognition and assemblage of the cases that as yet do not fall into accepted syndrome groups. Doubtless more or less definite causation and more or less definite toxico-pathologic mechanisms will ere long be established for Graves's and Raynaud's syndromes, as for Mitchell's erythromelalgia; and other syndrome groups among those described, may—like angioneurotic edema, hay fever, and migrain—receive limiting descriptions and specific names. I shall, in a future paper, attempt to point out some of the more or less constant associations that may serve as the bases for such diagnostic entities. But beyond all these will remain many vague and inconstant manifestations, recurring irregularly and

in varied association—differing from time to time in the same individual—to which the general term, vasomotor ataxia, will still apply; and which, without the clue afforded by a knowledge of this disorder, would be most puzzling. Yet, upon correct diagnosis depends their intelligent treatment. A patient alarmed by hemorrhage, gastric, pulmonary, or nasal, by sudden transient blindness, or by sudden general anasarca, may be soothed by a truthful assurance that there is no danger; the physician made unnecessarily anxious by the discovery of albumin or blood in a patient's urine may be relieved by the recognition of its origin; the substitutive symptoms occurring in the course of years in a given patient will be attributed to the one true cause, and not treated as so many different diseases. Though the spokes of the wheel are many, and at the periphery widely separated, there is but one hub, and that hub has but one center; and to this, not merely to spoke or to rim—to the central disorder and not merely to the peripheral symptoms—must the therapeutist direct his attention.

As to treatment, this must be largely individual and at first tentative. The congenital defect cannot be remedied, but its ill consequences may measurably be overcome. Chief to this end are hydrotherapeutic applications that will improve vascular tone and educate, from periphery to center, the responses to thermic and mechanical stimulation. Graduated douches and ablutions of alternating temperature (hot and cold), and effervescing thermal baths followed by cold water frictions, are among the best of these. Pneumotherapy, electrotherapy, and massage are also useful, and I anticipate good results from electric-light baths. When edematous and erythematous phenomena are most marked, ergot and barium chlorid are, with thymus extract, and adrenal preparations, both locally and systemic, among the medicaments often of service. When constrictive symptoms predominate, thyroid preparations, erythrol tetranitrate, sodium nitrate, and glonoin may palliate. Strychnin is a useful vasomotor tonic in some cases—but picrotoxin, which, if necessary, may safely be given to adults in doses of $\frac{1}{10}$ grain or even more—is perhaps the drug of greatest benefit in the majority of cases.[1] Judicious dietetic and hygienic regulations, supervision of

[1] Since reading this paper the girl, Sarah O'N., whose case was the first that I published (Philadelphia Polyclinic, June, 1892), has reported in good health; her hands exhibit color changes in hot and cold water, but she has no headache, no goiter, no tachycardia. The thyroid gland can easily be demonstrated, hence there is slight enlargement. Picrotoxin was the drug employed in her treatment, adrenal not having come into use at that time.

rest and exercise, with tonic psychic influences, are of prime importance. Usually the patient should be advised to drink water freely to avert autointoxication.

Recapitulation and Summary.

For description of cases the writer refers to his previous communications upon this subject and to the recent observations of Savill upon a subgroup manifesting acroparesthesia and acroasphyxia, etc. Attention is called to the condition of essential instability of the controlling (or taxic) apparatus of the vasomotor nervous system as a large factor in the defective reaction of the individual toward environmental changes, so that persons of the type described exhibit upon slight excitation (physical, chemical or psychic) certain phenomena which in other persons require causes of greater moment. These phenomena depend upon irregular, and sometimes widely-distributed contractions and dilatations of the capillaries and the smaller arteries (and veins?), and may be divided into three classes: (1) Those dependent upon excessive relaxation (dilator-excitation or constrictor-paresis) of the vessels, often with concomitant impairment of cardiac inhibition; (2) those dependent upon excessive constriction of vessels, usually with disturbances of cardiac inhibition also, but sometimes without definite cardiac phenomena clinically demonstrable; (3) those in which phenomena of the two opposite groups are commingled. The third group is the more common. Graves's disease presents an extreme type of the phenomena of excessive vascular dilatation, with paresis of cardiac inhibition. Its exciting causes are various, and its toxico-pathologic mechanism undetermined. Raynaud's disease presents an excessive type of vascular constriction, and of it the same may be said concerning undetermined exciting causes and toxico-pathologic mechanism. Between these two extremes are many varieties, differing much in severity and locality of symptoms: simple urticaria; angioneurotic edema; migraine of the spastic type and migraine of the paretic type; anomalous eruptions of various kinds; drug idiosyncrasies; hay fever; asthma; intermittent albuminuria; polyuria; tendencies to hemorrhage from various organs, to petechial and purpuric spots, and to small mucous or cutaneous varices and hematomata; minute cutaneous angiomata; paroxysmal tachycardia; and other more or less closely related

phenomena. As definite exciting causes and definite toxico-pathologic mechanisms are determined, definite nosologic groups may be separated and certain syndromes, like those of Graves and of Raynaud, made into diagnostic entities. Over and above these, however—and for the present, this is the most practical issue of these observations—will always remain many vague and ill-defined conditions arising in response to any one of a number of different stimuli, among which temperature, weather, endogenous and ectogenous noxæ, and emotion are most prominent. The symptoms may vary much in the same individual at different times; they may be manifested in the course of various acute and chronic diseases, confusing the diagnosis. With the clue afforded by the knowledge of vasomotor ataxia, however, the symptoms become clear, and intelligent treatment can be instituted. Hysteria, neurasthenia, and epilepsy bear close, but as yet undetermined relations to the condition, which may be predominant or apparently insignificant in their semeiology. The symptoms of the menopause are essentially vasomotor ataxic in character, but are a transient phase in the devolution of the female. Essential vasomotor ataxia is usually congenital—often affecting in different ways several members of one family; but at times the disorder seems to be acquired in sequence to disease or accident. Treatment must be largely dietetic, hygienic and psychic; with such medication, and such measures of physiologic therapy, as may be appreciated in the individual case.

DISCUSSION.

DR. PRINCE: I think the phenomena described by Dr. Cohen are interesting and in a way important ones, as they are found very frequently making up the symptom-complex of a large number of diseases. They belong to a class of symptomatic phenomena which are perversions of physiologic processes—that is to say, the phenomena themselves are physiologic, but the processes have become either enormously exaggerated or excited by abnormal associations. Dr. Putnam some time ago gave the name to some of them of "caricatures." If we look upon them in this light I think we can understand their pathology. What Dr. Cohen describes is practically what I once described under the name of "association neurosis." Clinically such perverted processes are of importance in that, after having become associated

together they form a group of recurring symptoms, and thus contribute a true functional disease. Not a few of the neuroses and psychoses have this pathology. Probably the only true functional diseases are of this nature.

DR. SACHS: It seems to me there is another point of view from which this whole subject must be regarded. I cannot see the benefit to be derived from separating this special group. We have been busy for ten years trying to differentiate this group, and, while I am fond of speculations, I think we should bear in mind the study of anatomic changes. At one end of the list Dr. Cohen has placed exophthalmic goiter and at the other end migraine. It seems to me we should be more interested in discovering the cause and acquiring actual concrete knowledge of the conditions underlying these various vasomotor disorders.

DR. JACOBI: Four weeks ago I saw a case of exophthalmic goiter in a patient forty-four years old who gave this history: She had been confined with her third child, and during her convalescence became frightened because her husband wanted to cohabit with her. She was so wrought up that she went into convulsions, and the next day presented the symptoms of exophthalmic goiter, from which she has been suffering these eleven years.

DR. COHEN: I agree thoroughly with the opinion that the conditions I have described are merely exaggerations of natural phenomena—that is to say, they would be normal when occurring under adequate excitation. Occurring as they do, they indicate the absence of the normal inhibitive or regulative power. In the paper itself, Dr. Sachs's objection to assembling rather than separating these phenomena has been anticipated and answered. Dr. Jacobi has pointed out forcibly how philosophic speculation is sometimes of advantage. There are a sufficient number of men making concrete, chemical and structural investigations, and nothing I may say or do will prevent them from continuing their good work; but, after all, we must gather and interpret the scattered data to appreciate their full significance. We must also learn something of the psychic causes of disease before we can apply intelligently that great remedy, psychic treatment. Such conditions as hysteria and neurasthenia can never be understood without the correlation of psychic and physical studies; and my observations are an attempt in that direction. Failure of inhibition is not an hypothetic, but an actual condition; and, moreover, anything that will enable us to establish and recognize classes of patients who are likely to exhibit certain group-symptoms will help us in studying both the gross and minute pathology and treatment of such conditions. Antemortem pathology is at least of equal importance with morbid anatomy.

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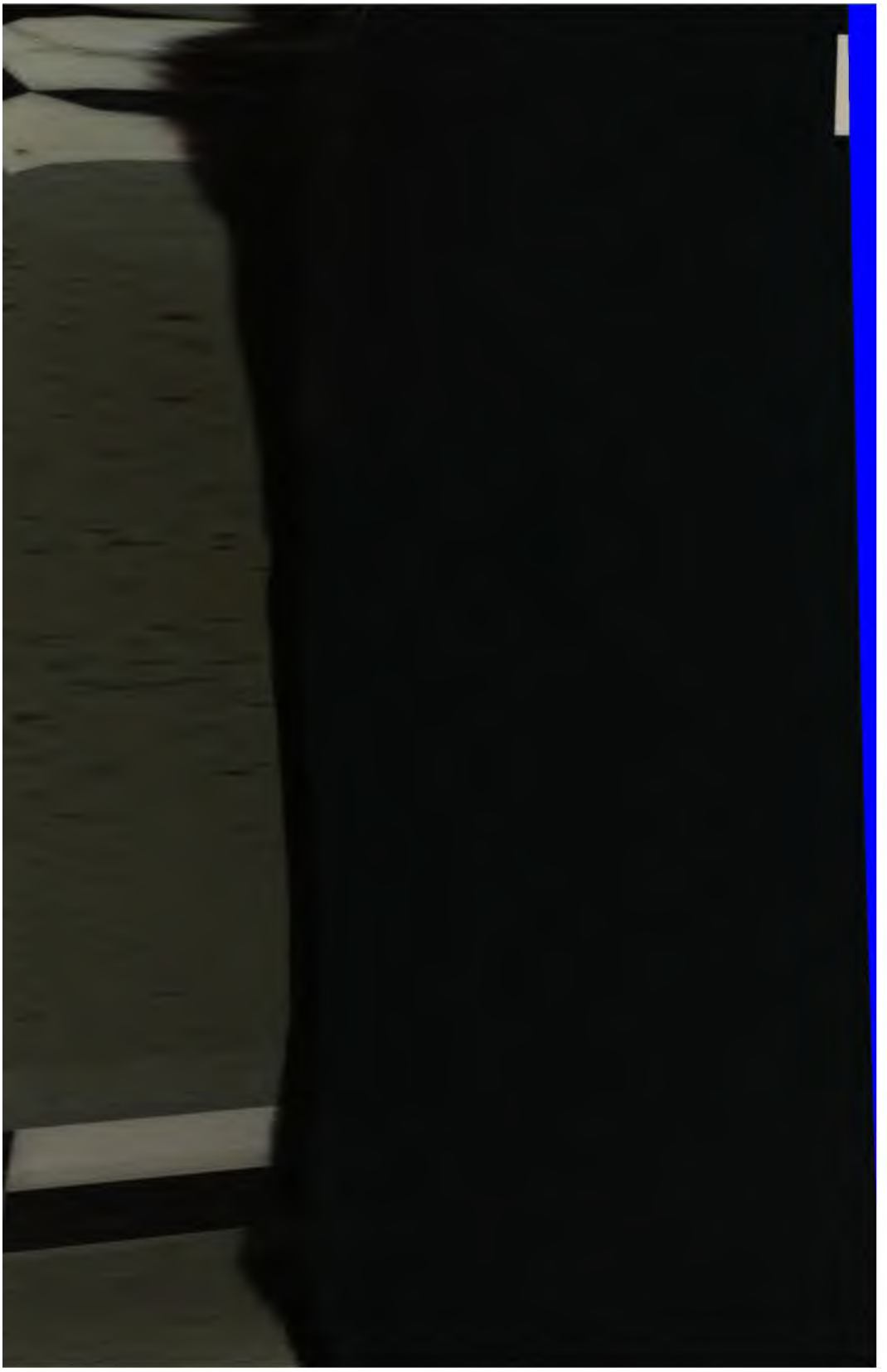
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